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(71) Applicant *(for all designated States except US)*: **MERCK & CO. INC.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BARROW, James, C.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **SELNICK, Harold, G.** [US/US]; 126 East lincoln Avenue, Rahway, NJ 07065-0907 (US). **NANTERMET, Philippe, G.** [FR/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **RITTLE, Kenneth, E.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **MCMASTERS, Daniel, R.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **STAUFFER, Shaun, R.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **BOLINGER, Stacey** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(74) Common Representative: **MERCK & CO. INC.**; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

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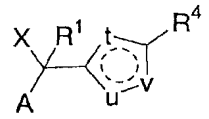
(54) Title: ANTICOAGULANT COMPOUNDS



(I)

(57) Abstract: Compounds of the invention are useful in inhibiting carboxypeptidase U and associated thrombotic occlusions having the structure (I) and pharmaceutically acceptable salts thereof, wherein t is N or N($R^{2''}$), u is C(R^3) or N($R^{2'}$), and v is C(R^2), N or N(R^2), provided that, 1) when t is N and u is C(R^3), then v is N(R^2); 2) when t is N and u is N($R^{2'}$), then v is C(R^2), and 3) when t is N($R^{2''}$) and u is C(R^3), then v is N or N(R^2).

TITLE OF THE INVENTION

ANTICOAGULANT COMPOUNDS

FIELD OF THE INVENTION

The present invention relates to novel compounds, and pharmaceutically acceptable salts thereof, which inhibit basic carboxypeptidases, more specifically carboxypeptidase U, and thus can be used in the prevention and treatment of diseases wherein inhibition of carboxypeptidase U is beneficial. In further aspects, the invention relates to compounds of the invention for use in therapy; to processes for preparation of such new compounds; to pharmaceutical compositions containing at least one compound of the invention, or a pharmaceutically acceptable salt thereof, as active ingredient; and to the use of the active compounds in the manufacture of medicaments for the medical use indicated above.

BACKGROUND OF THE INVENTION

Fibrinolysis is the result of a series of enzymatic reactions resulting in the degradation of fibrin by plasmin. The activation of plasminogen is the central process in fibrinolysis. The cleavage of plasminogen to produce plasmin is accomplished by the plasminogen activators, tissue-type plasminogen activator or urokinase-type plasminogen activator. Initial plasmin degradation of fibrin generates carboxy-terminal lysine residues that serves as high affinity binding sites for plasminogen. Since plasminogen bound to fibrin is much more readily activated to plasmin than free plasminogen this mechanism provides a positive feedback regulation of fibrinolysis.

One of the endogenous inhibitors to fibrinolysis is carboxypeptidase U (CPU). CPU is also known as plasma carboxypeptidase B, active thrombin activatable fibrinolysis inhibitor (TAFIa), carboxypeptidase R and inducable carboxypeptidase activity. CPU is formed during coagulation and fibrinolysis from its precursor proCPU by the action of proteolytic enzymes *e.g.* thrombin, thrombin-thrombomodulin complex or plasmin. CPU cleaves basic amino acids at the carboxy-terminal of fibrin fragments. The loss of carboxy-terminal lysines and thereby of lysine binding sites for plasminogen then serves to inhibit fibrinolysis.

By inhibiting the loss of lysine binding sites for plasminogen and thus increase the rate of plasmin formation, effective inhibitors of carboxypeptidase U would be expected to facilitate fibrinolysis.

Inhibitors of carboxypeptidase U are described in WO 00/66557, WO 00/66550, WO 00/66152, and WO 02/14285.

2-Mercaptomethyl-3-guanidinoethylthiopropanoic acid is reported as carboxypeptidase N inhibitor. More recently, this compound has been shown to inhibit CPU, Hendriks, D. *et al.*, Biochimica et Biophysica Acta, 1034 (1990) 86-92.

Guanidinoethylmercaptosuccinic acid is reported as carboxypeptidase N inhibitor. More recently, this compound has been shown to inhibit CPU, Eaton, D.L., *et al.*, The Journal of Biological Chemistry, 266 (1991) 21833-21838.

2-Benzyl-2-methylsuccinic acid, and imidazoles, are described as carboxypeptidase A inhibitors are described in Lee et al., Bioorganic & Medicinal Chemistry, Vol. 5, No. 10 pp. 1989-1998 (1997); Lee et al., Bioorganic & Medicinal Chemistry, 7 (1999) pp. 1755-1760; and Lee et al., Bioorganic & Medicinal Chemistry Letters, 11 (2001) pp. 1425-1427.

SUMMARY OF THE INVENTION

The invention includes compounds for inhibiting thrombus formation, and inhibiting embolus formation in a mammal, comprising a compound of the invention in a pharmaceutically acceptable carrier. The compounds can be added to blood, blood products, or mammalian organs in order to effect the desired inhibitions.

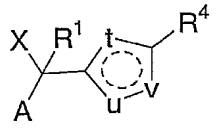
The invention also includes a compound for preventing or treating unstable angina, refractory angina, myocardial infarction, transient ischemic attacks, atrial fibrillation, thrombotic stroke, embolic stroke, deep vein thrombosis, disseminated intravascular coagulation, ocular build up of fibrin, and reocclusion or restenosis of recanalized vessels, atherosclerosis, adhesions, dermal scarring, cancer, fibrotic conditions, inflammatory diseases and those conditions which benefit from maintaining or enhancing bradykinin levels in a mammal, comprising a compound of the invention in a pharmaceutically acceptable carrier.

The invention also includes a method for reducing the thrombogenicity of a surface in a mammal by attaching to the surface, either covalently or noncovalently, a compound of the invention.

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

Compounds of the invention are useful as carboxypeptidase U inhibitors and have therapeutic value in for example, preventing coronary artery

disease. They are useful in preventing thrombosis and in thrombolytic therapy. The invention includes compounds having the following structure:



and pharmaceutically acceptable salts thereof, wherein

t is N or N($R^{2"}$), u is C(R^3) or N($R^{2'}$), and v is C(R^2), N or N(R^2),

provided that,

1) when t is N and u is C(R^3), then v is N(R^2),

2) when t is N and u is N($R^{2'}$), then v is C(R^2), and

3) when t is N($R^{2"}$) and u is C(R^3), then v is N or N(R^2);

A is

a) $COOR^5$,

b) tetrazole, or

c) a carboxylic acid isostere,

wherein R^5 is

1) hydrogen,

2) unsubstituted C_{1-8} alkyl, or

3) substituted C_{1-8} alkyl, wherein the alkyl substituent is selected from the group consisting of

i) aryl,

ii) heterocycle,

iii) $-NR^6R^7$,

iv) $-OR^6$, and

v) $-CHR^6OC(O)R^7$,

wherein R^6 and R^7 are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, and aryl;

X is

a) C_{1-6} alkyl, substituted with one or more basic groups, or

b) Y-W,

wherein Y is

1) (CR^8R^9),

2) (CR^8R^9)($CR^{10}R^{11}$),

3) $(CR^8R^9)(CR^{10}R^{11})(CR^{12}R^{13})$, or

4) a bond,

wherein R^8, R^{10}, and R^{12}, are independently selected from the group consisting of hydrogen, C 1-4 alkyl, OR^{14}, F, and $NR^{14}R^{15}$,

wherein R^{14} and R^{15} are independently selected from the group consisting of hydrogen and C_{1-4} alkyl, and

wherein R^9, R^{11}, and R^{13} are independently selected from the group consisting of hydrogen, F and C_{1-4} alkyl,

and wherein W is

1) a C_{3-7} cycloalkyl ring wherein at least one ring carbon atom is substituted with a basic group,

2) a 4- to 7-membered saturated or unsaturated heterocyclic ring, having 1-4 nitrogen ring atoms, wherein each ring carbon atom is independently unsubstituted or mono- or bi-substituted with a basic group, halogen, or C_{1-4} alkyl, or

3) a 6- or 10- membered aryl ring system, wherein at least one ring carbon atom is substituted with a basic group;

R^1 is selected from the group consisting of

a) hydrogen,

b) C_{1-4} alkyl,

c) OR^{16},

d) F, and

e) $NR^{16}R^{17}$,

wherein R^{16} and R^{17} are independently selected from the group consisting of hydrogen and C_{1-4} alkyl;

R^2 is selected from the group consisting of

a) hydrogen,

b) methyl,

c) phenyl, unsubstituted or independently mono- or di-substituted with a substitutent selected from the group consisting of halogen, phenyl, C_{1-4} alkyl, CF_3, CN, OCH_3, NH_2, NO_2, pyridine and pyrimidine,

d) C_{1-4} alkenyl, and

e) A^1-$(A^2)_{0-1}$-$(A^3)_{0-1}$-$(A^4)_{0-1}$-A^5, wherein

A^1 is C_{1-7} alkylene, wherein each carbon atom is independently unsubstituted or mono- or di-substituted with a substitutent selected from the group consisting of F, CF_3 and C_{1-4} alkyl,

A^2 is selected from the group consisting of C(O), C(O)NH, NHC(O), and -$NHSO_2$,

A^3 is a bond or C_{1-3} alkylene, where each carbon atom is independently unsubstituted or mono- or di-substituted with C_{1-4} alkyl,

A^4 is a bond, O, or OCH_2, and

A^5 is

1) phenyl, unsubstituted or independently mono- or di-substituted with a substitutent selected from the group consisting of halogen, phenyl, C_{1-4} alkyl, CF_3, CN, OCH_3 and NH_2,

2) pyridinyl,

3) naphthyl,

4) CF_3

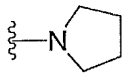
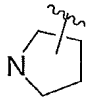
5) C_{1-5} alkyl,

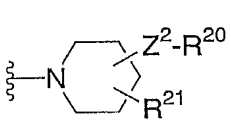
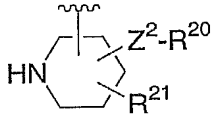
6) -$NR^{18}R^{19}$, wherein R^{18} and R^{19} are independently selected from the group of consisting of hydrogen and C_{1-4} alkyl,

7) OH,

8) COOH,

9) C_{3-10} carbocyclic ring system, unsubstituted or independently mono- or di-substituted with a substituent selected from the group consisting of NH_2 and C_{1-4} alkyl,

10)  or  , or

11)  or 

wherein Z^2 is a bond or C_{1-4} alkylene, R^{20} and R^{21} are independently selected from the group consisting of hydrogen, phenyl, CN or difluorophenyl;

$R^{2'}$ is selected from the group consisting of

a) hydrogen,

b) methyl,

c) phenyl, unsubstituted or independently mono- or di-substituted with a substitutent selected from the group consisting of halogen, phenyl, C_{1-4} alkyl, CF_3, CN, OCH_3, NH_2, NO_2, pyridine and pyrimidine,

d) C_{1-4} alkenyl, and

e) $A^{1'}$-$(A^{2'})_{0-1}$-$(A^{3'})_{0-1}$-$(A^{4'})_{0-1}$-$A^{5'}$, wherein

$A^{1'}$ is C_{1-7} alkylene, wherein each carbon atom is independently unsubstituted or mono- or di-substituted with a substitutent selected from the group consisting of F, CF_3 and C_{1-4} alkyl,

$A^{2'}$ is selected from the group consisting of C(O), C(O)NH, NHC(O), and -$NHSO_2$,

$A^{3'}$ is a bond or C_{1-3} alkylene, where each carbon atom is independently unsubstituted or mono- or di-substituted with C_{1-4} alkyl,

$A^{4'}$ is a bond, O, or OCH_2, and

$A^{5'}$ is

1) phenyl, unsubstituted or independently mono- or di-substituted with a substitutent selected from the group consisting of halogen, phenyl, C_{1-4} alkyl, CF_3, CN, OCH_3 and NH_2,

2) pyridinyl,

3) naphthyl,

4) CF_3

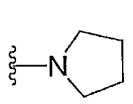
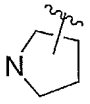
5) C_{1-5} alkyl,

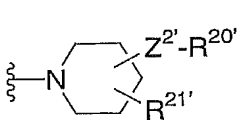
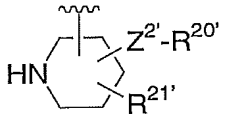
6) -$NR^{18'}R^{19'}$, wherein $R^{18'}$ and $R^{19'}$ are independently selected from the group of consisting of hydrogen and C_{1-4} alkyl,

7) OH,

8) COOH,

9) C_{3-10} carbocyclic ring system, unsubstituted or independently mono- or di-substituted with a substituent selected from the group consisting of NH_2 and C_{1-4} alkyl,

10)  or  , or

11)  or 

wherein $Z^{2'}$ is a bond or C_{1-4} alkylene, $R^{20'}$ and $R^{21'}$ are independently selected from the group consisting of hydrogen, phenyl, CN or difluorophenyl;

$R^{2"}$ is selected from the group consisting of

a) hydrogen,

b) methyl,

c) phenyl, unsubstituted or independently mono- or di-substituted with a substitutent selected from the group consisting of halogen, phenyl, C_{1-4} alkyl, CF_3, CN, OCH_3, NH_2, NO_2, pyridine and pyrimidine,

d) C_{1-4} alkenyl, and

e) $A^{1"}$-$(A^{2"})_{0-1}$-$(A^{3"})_{0-1}$-$(A^{4"})_{0-1}$-$A^{5"}$, wherein

$A^{1"}$ is C_{1-7} alkylene, wherein each carbon atom is independently unsubstituted or mono- or di-substituted with a substitutent selected from the group consisting of F, CF_3 and C_{1-4} alkyl,

$A^{2"}$ is selected from the group consisting of C(O), C(O)NH, NHC(O), and -$NHSO_2$,

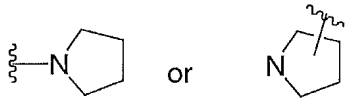
$A^{3"}$ is a bond or C_{1-3} alkylene, where each carbon atom is independently unsubstituted or mono- or di-substituted with C_{1-4} alkyl,

$A^{4"}$ is a bond, O, or OCH_2, and

$A^{5"}$ is

1) phenyl, unsubstituted or independently mono- or di-substituted with a substitutent selected from the group consisting of halogen, phenyl, C_{1-4} alkyl, CF_3, CN, OCH_3 and NH_2,

2) pyridinyl,
3) naphthyl,
4) CF_3
5) C_{1-5} alkyl,
6) $-NR^{18"}R^{19"}$, wherein $R^{18"}$ and $R^{19"}$ are independently selected from the group of consisting of hydrogen and C_{1-4} alkyl,
7) OH,
8) COOH,
9) C_{3-10} carbocyclic ring system, unsubstituted or independently mono- or di-substituted with a substituent selected from the group consisting of NH_2 and C_{1-4} alkyl,
10)



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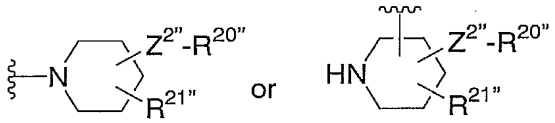


wherein $Z^{2"}$ is a bond or C_{1-4} alkylene, $R^{20"}$ and $R^{21"}$ are independently selected from the group consisting of hydrogen, phenyl, CN or difluorophenyl;

R^3 is
a) hydrogen,
b) unsubstituted or substituted C_{1-6} alkyl,
c) unsubstituted or substituted phenyl,
d) unsubstituted or substituted naphthyl, or
e) unsubstituted or substituted heterocycle,

wherein one or more substituents in substituted alkyl is independently selected from the group consisting of F, C_{1-6} alkyl, phenyl, naphthyl, and heterocyle, and one or more substituents in substituted phenyl, substituted naphthyl and substituted heterocycle is independently selected from the group consisting of phenyl, naphthyl, heterocyle, $-CF_3$, -CN, C_{1-6} alkyl, hydroxy, C_{1-4} alkoxy; halogen, $-NO_2$, $-NR^{23}R^{24}$, $-SO_2R^{23}$, $SO_2NR^{23}R^{24}$, $-CONR^{23}R^{24}$, or

COR^{23}, wherein R^{23} and R^{24} are independently selected hydrogen and C 1-4 alkyl; and

R^4 is

a) hydrogen,

b) unsubstituted or substituted C_{1-6} alkyl,

c) unsubstituted or substituted phenyl,

d) unsubstituted or substituted naphthyl,

e) unsubstituted or substituted heterocycle, or

f) unsubstituted or substituted C_{1-4} alkylenearyl,

wherein one or more substituents in substituted alkyl is independently selected from the group consisting of F, C_{1-6} alkyl, phenyl, naphthyl, and heterocyle, and one or more substituents in substituted phenyl, substituted naphthyl and substituted heterocycle is independently selected from the group consisting of phenyl, naphthyl, heterocyle, $-CF_3$, -CN, C_{1-6} alkyl, hydroxy, C_{1-4} alkoxy; halogen, $-NO_2$, $-NR^{25}R^{26}$, $-SO_2R^{25}$, $SO_2NR^{25}R^{26}$, $-CONR^{25}R^{26}$, or COR^{25}, wherein R^{25} and R^{26} are independently selected hydrogen and C_{1-4} alkyl.

In a class of compounds of the invention, A is COOH, R^1 is hydrogen, F or OH, R^3 is hydrogen, and R^4 is hydrogen.

In a subclass of this class of compounds, $R^{2'}$ is hydrogen and $R^{2"}$ is

a) phenyl, unsubstituted or substituted with C_{1-4} alkyl, or

b) $A^{1"}$-$A^{5"}$, wherein

$A^{1"}$ is C_{1-2} alkylene, wherein each carbon atom is independently unsubstituted or mono- or di-substituted with a substitutent selected from the group consisting of F, CF_3 and C_{1-4} alkyl , and

$A^{5"}$ is

1) phenyl, unsubstituted or independently mono- or di-substituted with a substitutent selected from the group consisting of halogen, phenyl, C_{1-4} alkyl, CF_3, CN, OCH_3 and NH_2, or

2) C_{1-5} alkyl.

In a group of the subclass,

X is

a) C_{1-4} alkyl, substituted with NH_2, or

b) Y-W,

wherein Y is $(CH_2)_{1-2}$

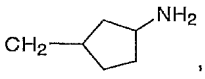
and wherein W is

1) a cyclopentyl substituted with NH_2,

2) a 4-7 membered saturated or unsaturated heterocyclic ring, having 1-4 nitrogen ring atoms, wherein each ring carbon atom is independently unsubstituted, mono- or bi-substituted with NH_2, CH_3 or Cl.

In a subgroup of the group, X is selected from the group consisting of

$(CH_2)_3NH_2$, $(CH_2)_4NH_2$, $(CH_2)_2CH(CH_3)CH_2NH_2$,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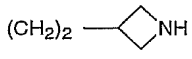
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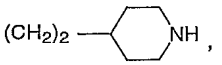
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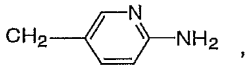
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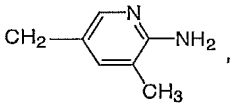
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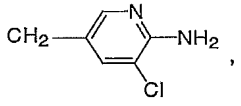
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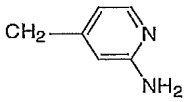

.

In a family of the subgroup, R^2 is selected from the group consisting of

hydrogen,

methyl,

phenyl, unsubstituted or substituted with C_{1-4} alkyl, NH_2, CN, NO_2, pyridine or pyrimidine,

C_{1-4} alkenyl and

A^1-$(A^2)_{0-1}$-$(A^3)_{0-1}$-$(A^4)_{0-1}$-A^5, wherein

A^1 is $(CH_2)_{1-7}$ or $CH(CH_3)$,

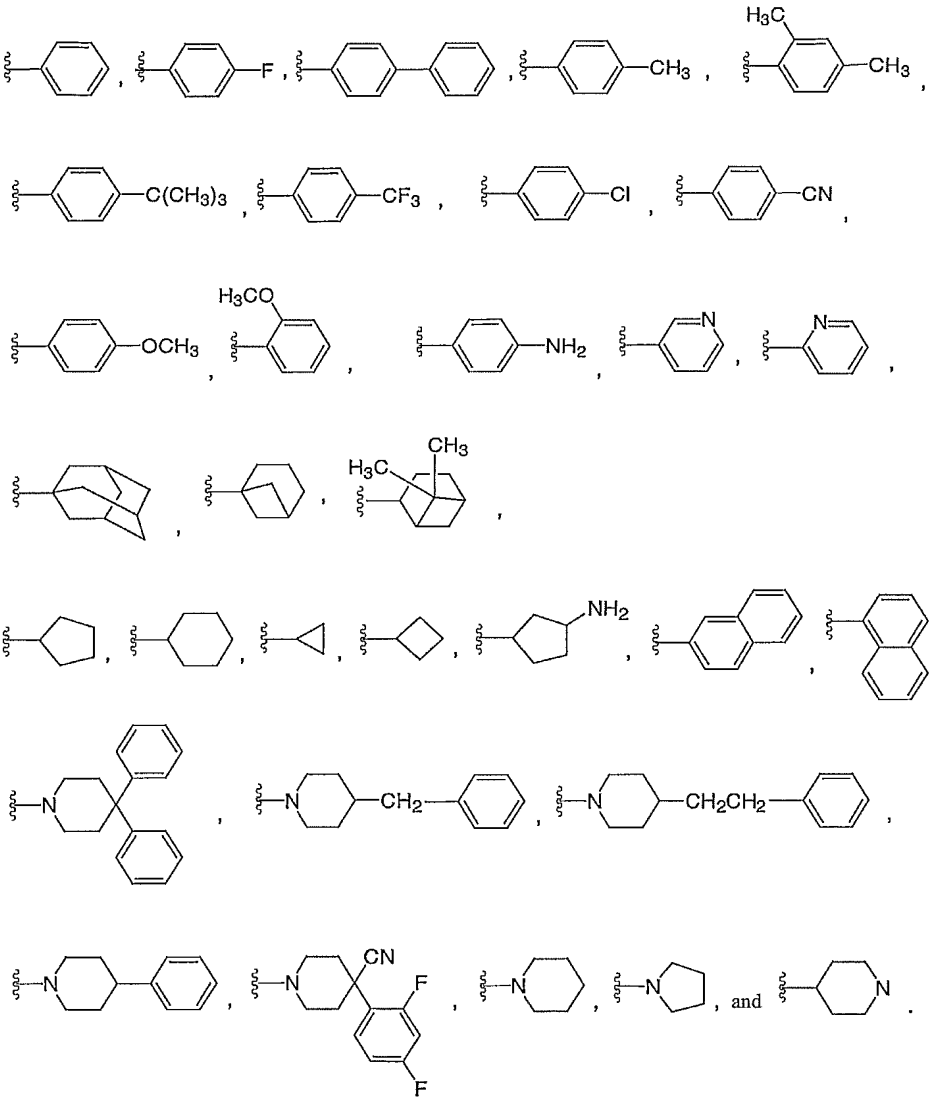
A^2 is selected from the group consisting of C(O), C(O)NH, NHC(O), and -$NHSO_2$,

A^3 is a bond, $(CH_2)_{1-3}$ or $C(CH_3)_2CH_2$,

A^4 is a bond, O, or OCH_2, and

A^5 is selected from the group consisting of

CF_3, CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, $CH(CH_2CH_3)_2$, $N(CH_2CH_3)_2$, $N(CH_3)_2$, NH_2, OH, COOH,



and

5

Specific examples of compounds of the invention include

3-(6-aminopyridin-3-yl)-2-(1*H*-imidazol-4-yl) propanoic acid

3-(6-amino-5-methylpyridin-3-yl)-2-(1H-imidazol-4-yl)propanoic acid

3-(6-amino-4-methylpyridin-3-yl)-2-(1H-imidazol-4-yl)propanoic acid

3-(6-amino-2-methylpyridin-3-yl)-2-(1H-imidazol-4-yl)propanoic acid

3-(6-amino-5-chloropyridin-3-yl)-2-(1H-imidazol-4-yl)propanoic acid

3-(2-aminopyridin-4-yl)-2-(1H-imidazol-4-yl)propanoic acid

3-(6-aminopyridin-2-yl)-2-(1H-imidazol-4-yl)propanoic acid

3-[(1R,3S)-3-aminocyclopentyl]-2-(1H-imidazol-4-yl)propanoic acid

3-[(1S,3R)-3-aminocyclopentyl]-2-(1H-imidazol-4-yl)propanoic acid

3-[(1S,3S)-3-aminocyclopentyl]-2-(1H-imidazol-4-yl)propanoic acid

3-[(1R,3R)-3-aminocyclopentyl]-2-(1H-imidazol-4-yl)propanoic acid

3-(4-aminocyclohexyl)-2-(1H-imidazol-4-yl)propanoic acid

3-(3-aminocyclohexyl)-2-(1H-imidazol-4-yl)propanoic acid

2-(1H-imidazol-4-yl)-4-pyrrolidin-3-ylbutanoic acid

2-(1H-imidazol-4-yl)-4-piperidin-3-ylbutanoic acid

2-(1H-imidazol-4-yl)-5-(1H-imidazol-5-yl)pentanoic acid

2-(1H-imidazol-4-yl)-5-(1H-imidazol-5-yl)butanoic acid

4-azetidin-3-yl-2-{1-[(4-methylphenyl)sulfonyl]-1H-imidazol-4-yl}butanoic acid

6-amino-2-(1-isopentyl-1*H*-imidazol-4-yl)hexanoic acid

5-amino-2-(1*H*-imidazol-4-yl)pentanoic acid

7-amino-2-(1*H*-imidazol-4-yl)heptanoic acid

6-methylamino-2-(1*H*-imidazol-4-yl)hexanoic acid

6-dimethylamino-2-(1*H*-imidazol-4-yl)hexanoic acid

3-(6-aminopyridin-3-yl)-2-(1-butyl-1*H*-imidazol-4-yl)propanoic acid

3-(6-aminopyridin-3-yl)-2-(1-benzyl-1*H*-imidazol-4-yl)propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(cyclohexylmethyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(3-phenylpropyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(cyclopropylmethyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(2-piperidin-4-ylethyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(2-phenylethyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(2-ethylbutyl)-1*H*-imidazol-4-yl]propanoic acid

2-(1-allyl-1*H*-imidazol-4-yl)-3-(6-aminopyridin-3-yl)propanoic acid

3-(6-aminopyridin-3-yl)-2-(1-isobutyl-1*H*-imidazol-4-yl)propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(2-methoxyethyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(cyclobutylmethyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-(1-methyl-1*H*-imidazol-4-yl)propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(2,2-difluoro-2-pyridin-2-ylethyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(3-methylbenzyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(4-methylbenzyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(4-cyanobenzyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(3-methoxybenzyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-(1-isopropyl-1*H*-imidazol-4-yl)propanoic acid

3-(6-aminopyridin-3-yl)-2-{1-[3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)propyl]-1*H*-imidazol-4-yl}propanoic acid

3-(6-aminopyridin-3-yl)-2-{1-[4-(trifluoromethyl) benzyl]-1*H*-imidazol-4-yl}propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(2-chlorobenzyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(4-chlorobenzyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(carboxymethyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(2-methylbenzyl)-1*H*-imidazol-4-yl]propanoic acid

4-({4-[2-(6-aminopyridin-3-yl)-1-carboxyethyl]-1*H*-imidazol-1-yl}methyl)benzoic

acid

3-(6-aminopyridin-3-yl)-2-[1-(3-chlorobenzyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-{1-[3-(benzyloxy) propyl]-1*H*-imidazol-4-yl}propanoic acid

4-{4-[2-(6-aminopyridin-3-yl)-1-carboxyethyl]-1*H*-imidazol-1-yl}butanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(pyridin-2-ylmethyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(3,3-dimethylbutyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(tetrahydrofuran-2-ylmethyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-{1-[2-(1*H*-pyrrol-1-yl)ethyl]-1*H*-imidazol-4-yl}propanoic acid

3-(6-aminopyridin-3-yl)-2-(1-ethyl-1*H*-imidazol-4-yl)propanoic acid

3-(6-aminopyridin-3-yl)-2-(1-propyl-1*H*-imidazol-4-yl)propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(tetrahydro-2*H*-pyran-2-ylmethyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(pyridin-3-ylmethyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(4,4,4-trifluorobutyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-(1-pentyl-1*H*-imidazol-4-yl)propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(4-nitrophenyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(4-cyanophenyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(2-cyanophenyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(2-nitrophenyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-(1-pyrimidin-2-yl-1*H*-imidazol-4-yl)propanoic acid

3-(6-aminopyridin-3-yl)-2-(1-hexyl-1*H*-imidazol-4-yl)propanoic acid

(2*R*)-3-(6-aminopyridin-3-yl)-2-[1-(2-cyclohexylethyl)-1*H*-imidazol-4-yl]propanoic acid

(2*R*)-2-{1-[2-(1-adamantyl)ethyl]-1*H*-imidazol-4-yl}-3-(6-aminopyridin-3-yl)propanoic acid

(2*R*)-3-(6-aminopyridin-3-yl)-2-[1-(2-cyclopropylethyl)-1*H*-imidazol-4-yl]propanoic acid

(2*R*)-3-(6-aminopyridin-3-yl)-2-{1-[2-(6,6-dimethylbicyclo[3.1.1]hept-2-yl)ethyl]-1*H*-imidazol-4-yl}propanoic acid

(2*R*)-3-(6-aminopyridin-3-yl)-2-(1-{2-[(1*S*,4*R*)-bicyclo[2.2.1]hept-2-yl]ethyl}-1*H*-imidazol-4-yl)propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(2-oxo-2-pyrrolidin-1-ylethyl)-1H-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-{1-[2-(benzylamino)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid

3-(6-aminopyridin-3-yl)-2-(1-{2-oxo-2-[(2-phenylethyl)amino]ethyl}-1*H*-imidazol-4-yl)propanoic acid

3-(6-aminopyridin-3-yl)-2-(1-{2-[(4-methoxyphenyl)amino]-2-oxoethyl}-1*H*-imidazol-4-

yl)propanoic acid

3-(6-aminopyridin-3-yl)-2-{1-[2-(methylamino)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid

3-(6-aminopyridin-3-yl)-2-{1-[2-oxo-2-(4-phenylpiperidin-1-yl)ethyl]-1*H*-imidazol-4-yl}propanoic acid

3-(6-aminopyridin-3-yl)-2-{1-[2-(ethylamino)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid

3-(6-aminopyridin-3-yl)-2-{1-[2-(diethylamino)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(2-anilino-2-oxoethyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(2-oxo-2-piperidin-1-ylethyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-(1-{2-oxo-2-[(3-phenylpropyl)amino]ethyl}-1*H*-imidazol-4-yl)propanoic acid

3-(6-aminopyridin-3-yl)-2-{1-[2-(1,1'-biphenyl-4-ylamino)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid

3-(6-aminopyridin-3-yl)-2-{1-[2-(2-naphthylamino)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid

3-(6-aminopyridin-3-yl)-2-{1-[2-(cyclohexylamino)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid

3-(6-aminopyridin-3-yl)-2-{1-[2-(dimethylamino)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(1-methyl-2-oxo-2-pyrrolidin-1-ylethyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-Aminopyridin-3-yl)-2-[1-(3,3-dimethyl-2-oxobutyl)-1H-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(2-oxo-2-phenylethyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-{1-[2-(4-chlorophenyl)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid

3-(6-aminopyridin-3-yl)-2-{1-[2-(4-fluorophenyl)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid

3-(6-aminopyridin-3-yl)-2-{1-[2-(1,1'-biphenyl-4-yl)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid

3-(6-aminopyridin-3-yl)-2-{1-[2-(4-cyanophenyl)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid

3-(6-aminopyridin-3-yl)-2-{1-[2-(4-methoxyphenyl)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid

3-(6-aminopyridin-3-yl)-2-{1-[2-(2-methoxyphenyl)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid

2-{1-[2-(1-adamantyl)-2-oxoethyl]-1*H*-imidazol-4-yl}-3-(6-aminopyridin-3-yl)propanoic acid

3-(6-aminopyridin-3-yl)-2-{1-[2-(4-methylphenyl)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid

2-{1-[2-(4-aminophenyl)-2-oxoethyl]-1*H*-imidazol-4-yl}-3-(6-aminopyridin-3-yl)propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(1-methyl-2-oxo-2-phenylethyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-{1-[2-(2-naphthyl)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid

3-(6-aminopyridin-3-yl)-2-{1-[2-(2,4-dimethyl phenyl)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid

3-(6-aminopyridin-3-yl)-2-(1-{2-oxo-2-[4-(trifluoromethyl) phenyl]ethyl}-1*H*-imidazol-4-yl)propanoic acid

(2*R*)-3-(6-aminopyridin-3-yl)-2-{1-[2-(4,4-diphenylpiperidin-1-yl)-2-oxoethyl]-1H-imidazol-4-yl}propanoic acid

(2*R*)-3-(6-aminopyridin-3-yl)-2-{1-[2-(benzylamino)-2-oxoethyl]-1H-imidazol-4-yl}propanoic acid

(2*R*)-3-(6-aminopyridin-3-yl)-2-{1-[2-(4-benzylpiperidin-1-yl)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid

(2*R*)-3-(6-aminopyridin-3-yl)-2-(1-{2-[4-cyano-4-(2,4-difluorophenyl) piperidin-1-yl]-2-oxoethyl}-1*H*-imidazol-4-yl)propanoic acid

(2*R*)-3-(6-aminopyridin-3-yl)-2-(1-{2-oxo-2-[4-(2-phenylethyl)piperidin-1-yl]ethyl}-1*H*-imidazol-4-yl)propanoic acid

(2*R*)-3-(6-aminopyridin-3-yl)-2-{1-[2-(4-*tert*-butylphenyl)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid

3-(6-aminopyridin-3-yl)-2-(1-methyl-1H-imidazol-2-yl)propanoic acid

3-(6-aminopyridin-3-yl)-2-(1-benzyl-1H-imidazol-2-yl)propanoic acid

3-(6-aminopyridin-3-yl)-2-(5-butyl-1H-imidazol-2-yl)propanoic acid

3-(6-aminopyridin-3-yl)-2-(5-benzyl-1H-imidazol-2-yl)propanoic acid

5-[2-(1H-imidazol-4-yl)-2-(2H-tetraazol-5-yl)ethyl]pyridin-2-amine di-trifluoroacetate

(2*R*)-3-(6-aminopyridin-3-yl)-2-(1-isopentyl-1*H*-imidazol-4-yl)propanoic acid

3-(6-Aminopyridin-3-yl)-2-fluoro-2-(1H-imidazol-4-yl)propanoic acid

2-[1-(4-aminophenyl)-1H-imidazol-4-yl]-3-(6-aminopyridin-3-yl)propanoic acid

3-(6-Aminopyridin-3-yl)-2-(1-pyridin-2-yl-1H-imidazol-4-yl)propanoic acid

3-(6-Aminopyridin-3-yl)-2-[1-(4-methylphenyl)-1H-imidazol-4-yl]propanoic acid

3-{6-[bis(tert-butoxycarbonyl)amino]pyridin-3-yl}-2-methyl-2-{1-[(4-methylphenyl)sulfonyl]-1H-imidazol-4-yl}propanoic acid

3-(6-Aminopyridin-3-yl)-2-hydroxy-2-(1H-imidazol-4-yl)propanoic acid

2-(6-Aminopyridin-3-yl)-3-(1H-imidazol-5-yl)propanoic acid

3-(6-amino-2,3,4,5-tetrahydropyridin-3-yl)-2-(1-isopentyl-1H-imidazol-4-yl)propanoic acid

3-(6-aminopyridin-3-yl)-2-(1H-imidazol-4-ylmethyl)propanoic acid

and pharmaceutically acceptable salts thereof

The inhibiting effect of the compounds of the invention was estimated using assays described in and based on Hendriks et al., Biochemica et Biophysica Acta, 1034 (1990) pp. 86-92, and Wang et al. The Journal of Biological Chemistry,

269, pp. 15937-15944 (1994). Carboxypeptidase U was isolated from human serum with rabbit thrombomodulin modified from reports by Hendriks et al 1990 and Wang et al 1994. ε-Aminocaproic acid (EACA) was added for stabilizing carboxypeptidase U during the isolation. Activity of carboxypeptidase U was measured using a synthetic peptide. Assay solutions were stopped by potato carboxypeptidase inhibitor. Ruthenium-labeled monoclonal antibody G2-10 and streptavidin-coated magnetic beads were added and electrochemiluminescence signals were detected using the M-series instrument (IGEN International, Inc.). Each of the compounds listed above was evaluated according to the assay and found to have an IC_{50} value in the range between 0.5 nM and 50 μM.

The activities shown by this assay indicate that the compounds of the invention are therapeutically useful for treating various conditions in patients suffering from unstable angina, refractory angina, myocardial infarction, transient ischemic attacks, atrial fibrillation, thrombotic stroke, embolic stroke, deep vein thrombosis, disseminated intravascular coagulation, and reocclusion or restenosis of recanalized vessels.

The compounds of the present invention, may have chiral centers and occur as racemates, racemic mixtures and as individual diastereomers, or enantiomers with all isomeric forms being included in the present invention. The compounds of the present invention may also have polymorphic crystalline forms, with all polymorphic crystalline forms being included in the present invention. The compounds of the invention also include tautomeric forms, with all tautomeric forms being included in the present invention.

When any variable occurs more than one time in any constituent or in formula I, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

Some abbreviations that may appear in this application are as follows:

ABBREVIATIONS

Designation	
AcOH	acetic acid
Bn	benzyl
$(Boc)_2O$	di-t-butyl dicarbonate
BuBr	butyl bromide

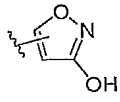
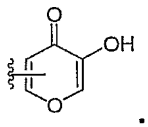
BuLi	butyl lithium
CF_3COOH	trifluoroacetic acid
CO	carbon monoxide
[CuTMEDA-(OH)]$_2Cl_2$	Di-u-hydroxo-bis[(N,N,N,N-tetramethylethylenediamine)copper(II)] chloride
DAST	diethylaminosulfurtrifluoride
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DiBAL	diisobutyl aluminum hydride
DMAP	dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DPPA	diphenylphosphoryl azide
dppp	1,3-bis(diphenylphosphino)propane
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
ES	electrospray mass spectrum
EtOAc	ethyl acetate
Et_2O	diethyl ether
Et_3N	triethyl amine
Et_3SiH	triethyl silane
HCl	hydrochloric acid
Het	heterocyclic group
$H_2NCH_2CH-(OMe)_2$	aminoacetaldehyde diethyl acetal
H_2NNH_2	hydrazine
HOAc	acetic acid
HOAT	1-hydroxy-7-azabenzotriazole
IPr_2Net	diisopropyl ethyl amine
IPrOH	2-propanol
IsoPentBr	isopenyl bromide
KOH	potassium hydroxide
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LHMDS	lithium (bistrimethylsilyl) amide

LiBr	lithium bromide
LiHMDS	lithium (bistrimethylsilyl) amide
LiOOH	lithium hydrogen peroxide
MCPBA	m-chloroperoxybenzoic acid
MeI	methyl iodide
MeOH	methanol
MeO_2CCN	methylcyanoformate
$(MeSO_2)_2O$	methane sulfonic anhydride
$MgSO_4$	magnesium sulfate
Ms_2O	methane sulfonic anhydride
n-BuLi	n-butyllithium
$N_3PO(Ph)_2$	diphenyl phosphoryl azide
$NaBH_4$	sodium borohydride
NaCN	sodium cyanide
NaH	sodium hydride
$NaHCO_3$	sodium hydrogen carbonate
NaHMDS	sodium (bistrimethylsilyl) amide
NaN_3	sodium azide
NaOH	sodium hydroxide
NaOMe	sodium methoxide
Na_2SO_4	sodium sulfate
$Na_2S_2O_3$	sodium thiosulfate
NCS	N-chlorosuccinimide
NHS	N-hydroxysuccinimide
NH_4Cl	ammonium chloride
p-$CH_3C_6H_4$-B(OH)2	4-methylphenyl boronic acid
$P(Ph)_3$	triphenyl phosphine
Pd(OAc)2	palladium acetate
Pd-C	palladium on activated carbon catalyst
Pd(OH)2	palladium hydroxide
$Pd(PPh)_3$	tetrakis triphenylphosphine palladium
$PhCH_3$	toluene
Ph_3PCHCO_2-Me	methyl-(triphenylphosphoranylidene)-acetate

Phth	phthalimidobutane
Piv	pivaloyl
PN	protected amino group
$POBr_3$	phosphorous oxybromide
(p-TolSO2)2-NF	N-fluoro-p-toluene sulfinamide
$SnCl_2$	tin(II) chloride
TEA	triethylamine
Tf_2O	trifluoromethane sulfonic anhydride
THF	tetrahydrofuran
Tr	triphenylmethyl
Ts	4-toluenesulfonyl
TsCl	p-toluenesulfonylchloride
SiO_2	silicon oxide
ZnBr2	zinc bromide
$Zn(CN)_2$	zinc cyanide

As used herein, except where noted, "alkyl" or "alkylene" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms; for example, "C_{1-6} alkyl", denotes alkyl having 1, 2, 3, 4, 5, or 6 carbon atoms. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, pentyl, and hexyl (Me is methyl, Et is ethyl, Pr is propyl, Bu is butyl). Unless otherwise specified, "propyl" denotes n-propyl or i-propyl; "butyl" denotes n-butyl, i-butyl, sec-butyl, or t-butyl. "Substituted" alkyl groups refer to groups having one or more defined substituents. The term "alkenyl" is intended to include both branched- and straight-chain unsaturated aliphatic hydrocarbon groups having the specified number of carbon atoms (e.g. ethenyl, propenyl, 1-butenyl, 2-butenyl); "substituted" alkenyl groups refer to groups having one or more defined substituents. The term "alkoxy" represents a linear or branched alkyl group of indicated number of carbon atoms attached through an oxygen bridge. The term "halogen", as used herein, means fluoro, chloro, bromo and iodo. The term "counterion" is used to represent a small, single negatively-charged species, such as chloride, bromide, hydroxide, acetate, trifluoroacetate, perchlorate, nitrate, benzoate, maleate, sulfate, tartrate, hemitartrate, benzene sulfonate, and the like.

The term "carboxylic isostere" includes an acidic group having a pKa of from about -5 to about 7, e.g. from about -1 to about 5, such as $-S(O)_2NHR_a$ (where R_a can be C_{1-4} alkyl), $-S(O)_2OH$, $-P(O)(OH)NH_2$, $-P(O)(OH)OCH_2CH_3$, -C(O)NH(CN),

The term "basic group" includes groups where the conjugate acid of said group has a pKa of from about 5 to about 15, such as an amino, amidino, guanidino, or pyridinyl.

The terms "cycloalkyl" and "cycloC_{3-7}alkyl" mean nonaromatic cyclic hydrocarbon groups having the specified number of carbon atoms and are intended to include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, and the like.

The term "aryl" as used herein except where noted, represents a stable 6- to 10-membered mono- or bicyclic ring system such as phenyl, or naphthyl, wherein at least one ring is aromatic. Unless otherwise specified, the aryl ring can be unsubstituted or substituted with one or more of $-CF_3$, -CN, C_{1-4} alkyl; hydroxy; C_{1-4} alkoxy; halogen, e.g. F, Cl, Br, or I; $-NO_2$; $-NR^aR^b$; $-SO_2R^a$; $SO_2NR^aR^b$; $-CONR^aR^b$; or COR^a, wherein R^a and R^b are independently selected hydrogen and C 1-4 alkyl.

The term "alkylenearyl", such as "C_{1-4} alkylenearyl" refers to a substituent which is an aryl group attached to the substituted atom with an alkylene linker, e.g. $-CH_2CH_2C_6H_5$.

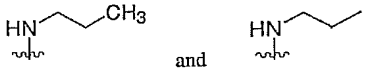
The terms "heterocycle", "heterocyclic", and " heterocyclyl" as used herein except where noted, represent a stable 5- to 7-membered monocyclic- or stable 8- to 11-membered fused bicyclic or stable 11- to 15-membered tricyclic ring system, any ring of which may be saturated, such as piperidinyl, partially saturated, or unsaturated, such as pyridinyl, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. Bicyclic unsaturated ring systems include bicyclic ring systems which may be partially

unsaturated or fully unsaturated. Partially unsaturated bicyclic ring systems include, for example, cyclopentenopyridinyl, benzodioxan, methylenedioxyphenyl groups. Especially useful are rings containing one oxygen or sulfur, one to four nitrogen atoms, or one oxygen or sulfur combined with one or two nitrogen atoms. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic groups include piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, thiadiazoyl, benzopyranyl, benzothiazolyl, benzoxazolyl, furyl, tetrahydrofuryl, tetrahydropyranyl, tetrazole, thienyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, and oxadiazolyl. Morpholino is the same as morpholinyl.

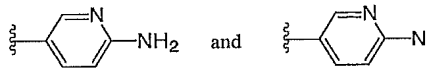
The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is an keto (i.e., =O), then 2 hydrogens on the atom are replaced.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

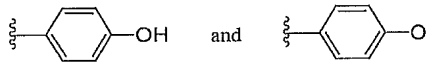
In this specification methyl substituents may be represented by  or  . For example, the structures



have equivalent meanings. Amino substituents may be represented by  or  . For example, the structures



have equivalent meanings. Hydroxy substituents may be represented by  or  . For example, the structures



have equivalent meanings.

The pharmaceutically-acceptable salts of the compounds of Formula I (in the form of water- or oil-soluble or dispersible products) include the conventional non-toxic salts such as those derived from inorganic acids, e.g. hydrochloric, hydrobromoic, sulfuric, sulfamic, phosphoric, nitric and the like, or the quaternary ammonium salts which are formed, e.g., from inorganic or organic acids or bases. Examples of acid addition salts include acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, sulfate, tartrate, thiocyanate, tosylate, and undecanoate. Base salts include ammonium salts, alkali metal salts such as sodium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth. Also, the basic nitrogen-containing groups may be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others.

Carboxypeptidase U Inhibitors - Therapeutic Uses- Method of Using

Anticoagulant therapy is indicated for the treatment and prevention of a variety of thrombotic conditions, particularly coronary artery and cerebrovascular

disease. Those experienced in this field are readily aware of the circumstances requiring anticoagulant therapy. The term "patient" used herein is taken to mean mammals such as primates, including humans, sheep, horses, cattle, pigs, dogs, cats, rats, and mice.

Carboxypeptidase U inhibition is useful not only in the anticoagulant therapy of individuals having thrombotic conditions, but is useful whenever inhibition of blood coagulation is required such as to prevent coagulation of stored whole blood and to prevent coagulation in other biological samples for testing or storage. Thus, the carboxypeptidase U inhibitors can be added to or contacted with any medium containing or suspected of containing carboxypeptidase U and in which it is desired that blood coagulation be inhibited, e.g., when contacting the mammal's blood with material selected from the group consisting of vascular grafts, stents, orthopedic prosthesis, cardiac prosthesis, and extracorporeal circulation systems.

Compounds of the invention are useful for treating or preventing venous thromboembolism (e.g. obstruction or occlusion of a vein by a detached thrombus; obstruction or occlusion of a lung artery by a detached thrombus), cardiogenic thromboembolism (e.g. obstruction or occlusion of the heart by a detached thrombus), arterial thrombosis (e.g. formation of a thrombus within an artery that may cause infarction of tissue supplied by the artery), atherosclerosis (e.g. arteriosclerosis characterized by irregularly distributed lipid deposits) in mammals, and for lowering the propensity of devices that come into contact with blood to clot blood.

Examples of venous thromboembolism which may be treated or prevented with compounds of the invention include obstruction of a vein, obstruction of a lung artery (pulmonary embolism), deep vein thrombosis, thrombosis associated with cancer and cancer chemotherapy, thrombosis inherited with thrombophilic diseases such as Protein C deficiency, Protein S deficiency, antithrombin III deficiency, and Factor V Leiden, and thrombosis resulting from acquired thrombophilic disorders such as systemic lupus erythematosus (inflammatory connective tissue disease). Also with regard to venous thromboembolism, compounds of the invention are useful for maintaining patency of indwelling catheters.

Examples of cardiogenic thromboembolism which may be treated or prevented with compounds of the invention include thromboembolic stroke (detached thrombus causing neurological affliction related to impaired cerebral blood supply),

cardiogenic thromboembolism associated with atrial fibrillation (rapid, irregular twitching of upper heart chamber muscular fibrils), cardiogenic thromboembolism associated with prosthetic heart valves such as mechanical heart valves, and cardiogenic thromboembolism associated with heart disease.

Examples of arterial thrombosis include unstable angina (severe constrictive pain in chest of coronary origin), myocardial infarction (heart muscle cell death resulting from insufficient blood supply), ischemic heart disease (local anemia due to obstruction (such as by arterial narrowing) of blood supply), reocclusion during or after percutaneous transluminal coronary angioplasty, restenosis after percutaneous transluminal coronary angioplasty, occlusion of coronary artery bypass grafts, and occlusive cerebrovascular disease. Also with regard to arterial thrombosis, compounds of the invention are useful for maintaining patency in arteriovenous cannulas.

Examples of atherosclerosis include arteriosclerosis.

Examples of devices that come into contact with blood include vascular grafts, stents, orthopedic prosthesis, cardiac prosthesis, and extracorporeal circulation systems

The carboxypeptidase U inhibitors of the invention are also useful for angiogenesis and for treating cancer diseases by inhibiting coagulation and moderating blood vessel formation. Such diseases include the proliferation of tumor cells and the pathologic neovascularization (or angiogenesis) that supports solid tumor growth. The instant compounds inhibit tumor angiogenesis, thereby affecting the growth of tumors (J. Rak et al. Cancer Research, 55:4575-4580, 1995). The instant compounds are also useful in combination with known anti-cancer agents. Such known anti-cancer agents include the following: estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors, HIV protease inhibitors, reverse transcriptase inhibitors, kinase insert domain receptor (KDR) kinase inhibitors (such as those disclosed in patent publications WO 0129025, WO 0117995 and U.S. Patent 6306874), and other angiogenesis inhibitors.

They are also useful for promoting wound healing. Carboxypeptidase U inhibitors are also useful for treating pain and inflammation, particularly arthritis and related arthritic conditions. Carboxypeptidase U inhibitors are also useful in thrombolytic therapy, especially when combined with thrombolytic agents such as

plasminogen activators or streptokinase to achieve synergistic effects in the treatment of various vascular pathologies.

Carboxypeptidase U inhibitors are also useful in the treatment of atherosclerosis. Atherosclerosis is a common condition in subjects suffering from peripheral vascular disease, insulin resistance and the group of conditions commonly referred to as 'Syndrome X. Syndrome X is a term often used to group together a number of interrelated diseases. The first stage of syndrome X consists of insulin resistance, abnormal cholesterol and triglyceride levels, obesity and hypertension. Any one of these conditions may be used to diagnose the start of Syndrome X. The disease may then progress with one condition leading to the development of another in the group. For example insulin resistance is associated with high lipid levels, hypertension and obesity. The disease then cascades, with the development of each additional condition increasing the risk of developing more serious diseases. This can progress to the development of diabetes, kidney disease and heart disease. These diseases may lead to stroke, myocardial infarction and organ failure.

Carboxypeptidase U inhibitors are also effective in inhibiting tumor maturation and progression. Metastasis is a complex and multifactorial process which is not yet fully understood. Accordingly, whilst not wishing to be bound by any theory, it is believed that the haemostatic system is involved at several levels of cancer pathology, including neovascularization, shedding of cells from the primary tumor, invasion of the blood supply, adherence to the vessel wall and growth at the metastatic site. It is thought that the efficacy of carboxypeptidase U inhibitors stems from an ability to reduce fibrin deposition around solid tumors and thereby inhibit the above processes.

The carboxypeptidase U inhibitors can also be co-administered with suitable anticoagulants (e.g. warfarin, unfractionated heparin, low molecular weight heparin, a thrombin inhibitor, a Factor Xa inhibitor) and/or suitable antiplatelet agents, including, but not limited to, fibrinogen receptor antagonists (e.g. to treat or prevent unstable angina or to prevent reocclusion after angioplasty and restenosis), aspirin, platelet inhibitors (e.g. dipyridamole), inhibitors of ADP-induced platelet aggregation (e.g. clopidogrel) or platelet aggregation inhibitors such as ticlopidine, to achieve synergistic effects in the treatment of various vascular pathologies, or lipid lowering agents including antihypercholesterolemics (e.g. HMG CoA reductase inhibitors such as lovastatin and simvastatin, HMG CoA synthase inhibitors, etc.) to treat or prevent atherosclerosis. For example, patients suffering from coronary artery

disease, and patients subjected to angioplasty procedures, would benefit from coadministration of fibrinogen receptor antagonists and carboxypeptidase U inhibitors. Also, carboxypeptidase U inhibitors enhance the efficiency of tissue plasminogen activator-mediated thrombolytic reperfusion. Carboxypeptidase U inhibitors may be administered first following thrombus formation, and tissue plasminogen activator or other plasminogen activator is administered thereafter.

Typical doses of carboxypeptidase U inhibitors of the invention in combination with other suitable anti-platelet agents, anticoagulation agents, or thrombolytic agents may be the same as those doses of carboxypeptidase U inhibitors administered without coadministration of additional anti-platelet agents, anticoagulation agents, or thrombolytic agents, or may be substantially less that those doses of carboxypeptidase U inhibitors administered without coadministration of additional anti-platelet agents, anticoagulation agents, or thrombolytic agents, depending on a patient's therapeutic needs.

The carboxypeptidase U inhibitors of the invention can be administered in such oral forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixers, tinctures, suspensions, syrups, and emulsions. Likewise, they may be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using forms well known to those of ordinary skill in the pharmaceutical arts. An effective but non-toxic amount of the compound desired can be employed as an anti-aggregation agent. For treating ocular build up of fibrin, the compounds may be administered intraocularly or topically as well as orally or parenterally.

The carboxypeptidase U inhibitors can be administered in the form of a depot injection or implant preparation which may be formulated in such a manner as to permit a sustained release of the active ingredient. The active ingredient can be compressed into pellets or small cylinders and implanted subcutaneously or intramuscularly as depot injections or implants. Implants may employ inert materials such as biodegradable polymers or synthetic silicones, for example, Silastic, silicone rubber or other polymers manufactured by the Dow-Corning Corporation.

The carboxypeptidase U inhibitors can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

The carboxypeptidase U inhibitors may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The carboxypeptidase U inhibitors may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinlypyrrolidone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxyethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the carboxypeptidase U inhibitors may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels.

The dosage regimen utilizing the carboxypeptidase U inhibitors is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the condition.

Oral dosages of the carboxypeptidase U inhibitors, when used for the indicated effects, will range between about 0.01 mg per kg of body weight per day (mg/kg/day) to about 30 mg/kg/day, for example 0.025-7.5 mg/kg/day, more specifically 0.1-2.5 mg/kg/day, and even more specifically 0.1-0.5 mg/kg/day (unless specificed otherwise, amounts of active ingredients are on free base basis). An 80 kg patient, for example, would receive between about 0.8 mg/day and 2.4 g/day, for example 2-600 mg/day, specifically 8-200 mg/day, more specifically 8-40 mg/kg/day. A suitably prepared medicament for once a day administration would thus contain between about 0.8 mg and 2.4 g, for example 2 mg and 600 mg, specifically 8 mg and 200 mg, and more specifically 8 mg and 40 mg, e.g., 8 mg, 10 mg, 20 mg and 40 mg. The carboxypeptidase U inhibitors may also be administered in divided doses of two, three, or four times daily. For administration twice a day, a suitably prepared medicament would contain between about 0.4 mg and 4 g, for example 1 mg and 300 mg, specifically 4 mg and 100 mg, and more specifically 4 mg and 20 mg, e.g., 4 mg, 5 mg, 10 mg and 20 mg.

Intravenously, the patient would receive the active ingredient in quantities sufficient to deliver between about 0.025-7.5 mg/kg/day, for example 0.1-2.5 mg/kg/day, specifically 0.1-0.5 mg/kg/day. Such quantities may be administered in a number of suitable ways, e.g. large volumes of low concentrations of active ingredient during one extended period of time or several times a day, low volumes of high concentrations of active ingredient during a short period of time, e.g. once a day. Typically, a conventional intravenous formulation may be prepared which contains a concentration of active ingredient of between about 0.01-1.0 mg/ml, e.g. 0.1 mg/ml, 0.3 mg/ml, and 0.6 mg/ml, and administered in amounts per day of between about 0.01 ml/kg patient weight and 10.0 ml/kg patient weight, e.g. 0.1 ml/kg, 0.2 ml/kg, 0.5 ml/kg. In one example, an 80 kg patient, receiving 8 ml twice a day of an intravenous formulation having a concentration of active ingredient of 0.5 mg/ml, receives 8 mg of active ingredient per day. Glucuronic acid, L-lactic acid, acetic acid, citric acid or any pharmaceutically acceptable acid/conjugate base with reasonable buffering capacity in the pH range acceptable for intravenous administration may be used as buffers. The choice of appropriate buffer and pH of a formulation, depending on solubility of the drug to be administered, is readily made by a person having ordinary skill in the art.

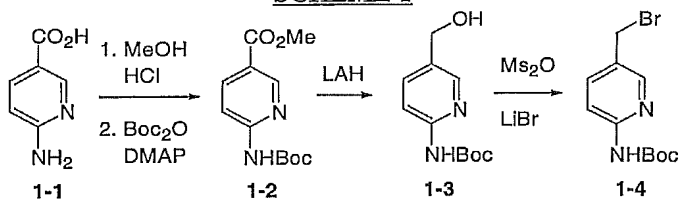
The compounds can also be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, or course, be continuous rather than intermittent throughout the dosage regime.

The carboxypeptidase U inhibitors are typically administered as active ingredients in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixers, syrups and the like, and consistent with convention pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders,

lubricants, distintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn-sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch methyl cellulose, agar, bentonite, xanthan gum and the like.

SCHEME 1



methyl 6-[(tert-butoxycarbonyl)amino]nicotinate (**1-2**)

Through a 0 °C solution of 10.1 g (73.1 mmol) 6-aminonicotinic acid in 250 mL MeOH was passed HCl gas for 10 minutes. The ice bath was removed and the reaction mixture was stirred at 50 °C for 20 h. The reaction mixture was concentrated in vacuo. The residue was concentrated from methanol (3x) and from dichloromethane (2x) to give methyl 6-aminonicotinate hydrochloride (15 g) which was used as is in the next step. To a solution of 13.8 g (73.1 mmol) methyl 6-aminonicotinate hydrochloride in 250 mL dichloromethane and 15.3 mL (109.7 mmol) triethylamine was added 447 mg (3.6 mmol) 4-dimethylaminopyridine and 17.6 g (80.4 mmol) di-tert-butyl-dicarbonate. The reaction mixture was stirred at room temperature for 20 h and the reaction progress was evaluated by TLC. Further additions of triethylamine and di-tert-butyl-dicarbonate over the next 48 h allowed the reaction to progress to ca. 75% completion by TLC. The reaction mixture was concentrated in vacuo and purified by flash chromatography (silica gel, hexane to 75% Et_2O in hexane) to give 11.3 g methyl 6-[(tert-butoxycarbonyl)amino]nicotinate (**1-2**) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (br s, 1H); 8.98 (d, 1H, *J*= 2.2 Hz); 8.27 (dd, 1H, *J*= 9, 2.2 Hz); 8.08 (d, 1H, *J*= 9 Hz); 3.92 (s, 3H); 1.6 (s, 9H).

tert-butyl 5-(hydroxymethyl)pyridin-2-ylcarbamate (**1-3**)

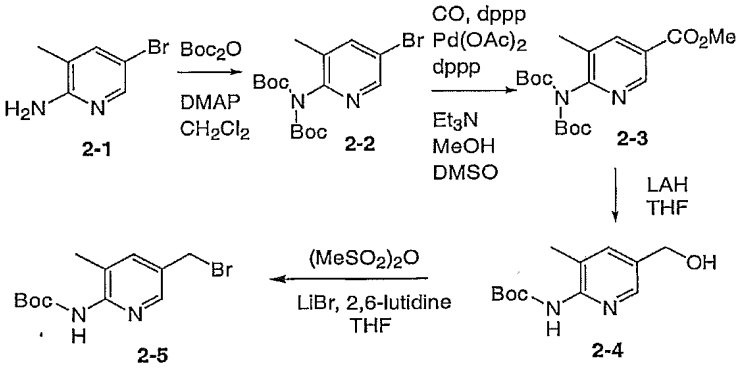
To a solution of 20 g (75.1 mmol) methyl 6-[(tert-butoxycarbonyl)amino]nicotinate (**1-2**) in 500 mL THF cooled to 0 °C was added 120.2 mL (120.2 mmol) 1M LAH in THF dropwise over 20 min. The reaction mixture is stirred at 0 °C for 1h and carefully poured into aqueous sodium potassium tartrate. After vigorous stirring for 90 minutes, the organic layer was separated and the aqueous layer was back extracted with diethyl ether. The combined organic layers were dried on magnesium sulfate, concentrated in vacuo, and purified by flash chromatography (silica gel, 50% to 75% EtOAc in hexane) to give 9 g tert-butyl 5-(hydroxymethyl)pyridin-2-ylcarbamate (**1-3**) as a pale yellow solid. ^{1}H NMR (400

MHz, $CDCl_3$) δ 8.24 (d, 1H, *J*= 2.3 Hz); 7.96 (d, 1H, *J*= 9 Hz); 7.69 (dd, 1H, *J*= 9, 2.3 Hz); 7.60 (br s, 1H); 4.66 (d, 2H, *J*= 5.7 Hz); 1.68 (t, 1H, *J*= 5.7 Hz); 1.53 (s, 9H).

tert-butyl 5-(bromomethyl)pyridin-2-ylcarbamate (**1-4**)

To a solution of 9.92 g (44.2 mmol) of tert-butyl 5-(hydroxymethyl) pyridin-2-ylcarbamate (**1-3**) in 220 mL THF cooled to 0 °C was added 10.3 mL (88.4 mmol) lutidine, 7.68 g (88.4 mmol) lithium bromide and 15.41 g (88.4 mmol) methanesulfonic anhydride. Continued stirring in ice bath for 5 min, then warmed to 55 °C for 3.5 h. Poured reaction mixture into aqueous saturated sodium bicarbonate and extracted 3x with ethyl acetate/diethyl ether (1/1). The combined organic extracts were washed with water (1x), brine (1x), dried over sodium sulfate, filtered and concentrated in vacuo. The wet residue was treated with acetonitrile and concentrated (3x) resulting in a slurry which, after filtration, gave 10.51 g (82.7% yield) of tert-butyl 5-(bromomethyl)pyridin-2-ylcarbamate (**1-4**) as a fine white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, 1H, *J*= 2.4 Hz); 7.95 (d, 1H, *J*= 8.6 Hz); 7.86 (br s, 1H); 7.69 (dd, 1H, *J*= 8.7, 2.4 Hz); 4.45 (s, 2H); 1.54 (s, 9H).

SCHEME 2



Di-(*tert*-butyl)-5-bromo-3-methylpyridin-2-ylimidodicarbonate (**2-2**)

To a solution of 5-bromo-3-methylpyridin-2-amine (12 g, 0.064 mol) and 4-dimethylaminopyridine (3.9 g, 0.032 mol) in methylene chloride (780 mL), cooled to 0°C, was added dropwise a solution of di-*tert*-butyl dicarbonate (37 g, 0.17 mol) in methylene chloride (100 mL). The reaction mixture was stirred at room

temperature overnight and concentrated. Flash chromatography (silica gel, hexane-ethyl acetate, 92:8-88:12) gave di-(*tert*-butyl)-5-bromo-3-methylpyridin-2-ylimidodicarbonate (**2-2**). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.40 (m, 1H), 7.73 (m, 1H), 2.22 (s, 3H), 1.41 (s, 18H).

Methyl-6-[bis(*tert*-butoxycarbonyl)amino]-5-methylnicotinate (**2-3**)

A solution of di-(*tert*-butyl)-5-bromo-3-methylpyridin-2-ylimidodicarbonate (**2-2**) (10 g, 0.026 mol) and triethylamine (14.5 mL, 0.104 mol) in methanol (359 mL) and methyl sulfoxide (186 mL) was purged with carbon monoxide gas for 8 minutes. Palladium (II) acetate (1.2 g, 0.0052 mol) and 1,3-bis(diphenylphosphino)propane (2.1 g, 0.0052 mol) were added and the reaction mixture was stirred at 80°C under a carbon monoxide atmosphere overnight. Ether and water were added, the reaction was filtered through celite and extracted with ether. The combined organic layers were washed with saturated sodium bicarbonate solution and brine, dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (silica gel, hexane-ethyl acetate, 95:5-55:45) gave methyl-6-[bis(*tert*-butoxycarbonyl)amino]-5-methylnicotinate (**2-3**); ^{1}H NMR ($CDCl_3$, 400 MHz) 8.95 (m, 1H), 8.19 (m, 1H), 3.96 (s, 3H), 2.29 (s, 3H), 1.40 (s, 18H).

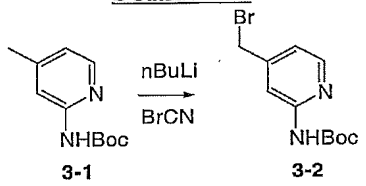
Tert-butyl-5-(hydroxymethyl)-3-methylpyridin-2-ylcarbamate (**2-4**)

To a solution of methyl-6-[bis(*tert*-butoxycarbonyl)amino]-5-methylnicotinate (**2-3**) (2.0 g, 5.46 mmol) in tetrahydrofuran (20 mL), cooled to 0°C was added lithium aluminum hydride (1.0M in tetrahydrofuran, 16.4 mL, 16.4 mmol) dropwise. The reaction mixture was stirred at 0°C for 1 hour, quenched successively with water (1.28 mL), 15% sodium hydroxide solution (1.28 mL) and water (2.46 mL) and stored in the refrigerator overnight. Filtration and solvent evaporation gave *tert*-butyl-5-(hydroxymethyl)-3-methylpyridin-2-ylcarbamate (**2-4**); ^{1}H NMR ($DMSO_{d6}$, 400 MHz) δ 9.02 (s, 1H), 8.12 (s, 1H), 7.54 (s, 1H), 4.46 (s, 2H), 2.18 (s, 3H), 1.44 (s, 9H).

Tert-butyl-5-(bromomethyl)-3-methylpyridin-2-ylcarbamate (**2-5**)

To a suspension of *tert*-butyl-5-(hydroxymethyl)-3-methylpyridin-2-ylcarbamate (**2-4**) (1.3 g, 5.45 mmol), 2,6-lutidine (1.3 mL, 10.9 mmol) and lithium bromide (0.95 g, 10.9 mmol) in tetrahydrofuran (25 mL), cooled to 0°C was added methanesulfonic anhydride (1.9 g, 10.9 mmol). The reaction mixture was heated to 55°C for 1.5 hours, quenched with saturated sodium bicarbonate solution and extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. Trituration of the resulting solid with acetonitrile gave *tert*-butyl-5-(bromomethyl)-3-methylpyridin-2-ylcarbamate (**2-5**); ^{1}H NMR (DMSO, 400 MHz) δ 9.18 (s, 1H), 8.27 (s, 1H), 7.70 (s, 1H), 4.70 (s, 2H), 2.18 (s, 3H), 1.45 (s, 9H).

SCHEME 3



3-1 **3-2**

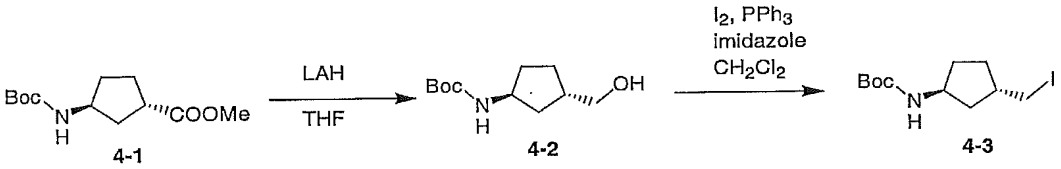
U.S. Patent 5,852,045 coumns 49-50, describes a procedure for preparing **3-2**.

tert-butyl 4-(bromomethyl)pyridin-2-ylcarbamate (**3-2**)

To a solution of tert-butyl 4-methylpyridin-2-ylcarbamate (**3-1**) (20 g, 96 mmol) (obtained from 2-amino-4-methyl-pyridine and di-tertbutyl-dicarbonate) in 175 mL THF cooled to –78 °C was added nBuLi (84 mL, 201.7 mmol, 2.4 M in hexane) dropwise. The reaction mixture was warmed to 0 °C and stirred at 0 °C for 30 min. The reaction mixture was cannulated to a –78 °C cooled addition funnel mounted on the side arm of a 2L flask containing cyanogen bromide (81.4 g, 768.3 mmol) in 500 mL THF cooled to –100 °C. The cannulated cooled slurry was added dropwise to the cyanogen bromide/THF mixture while keeping the internal temperature below or at –100 °C and while maintaining vigorous stirring. At the end of the addition the reaction mixture was stirred at –100 °C for an extra 30 min. Water (500 mL) was added and the reaction mixture is extracted with EtOAc. The organic

layer was washed with 10% $KHSO_4$, brine and dried over sodium sulfate. Concentration in vacuo and purification by flash chromatography (silica gel, 10% to 45% EtOAc in hexane) provided tert-butyl 4-(bromomethyl)pyridin-2-ylcarbamate (**3-2**) (23.4 g) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, 1H, *J*= 5.3 Hz); 8.00 (br s, 1H); 7.93 (br s, 1H); 6.90 (dd, 1H, *J*= 5.3, 1.5 Hz); 4.38 (s, 2H); 1.55 (s, 9H).

SCHEME 4



Tert-butyl-(1S, 3S)-3-hydroxymethyl)cyclopentylcarbamate **(4-2)**

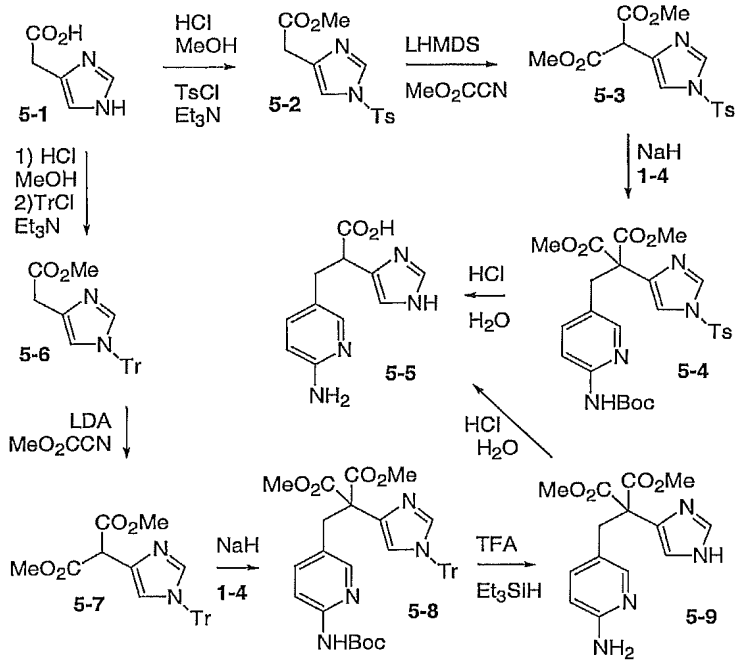
To a solution of methyl-(1S, 3S)-3-[{*tert*-butoxycarbonyl}amino]cyclopentane carboxylate (350 mg, 1.4 mmol) in tetrahydrofuran (5 mL), cooled to 0°C was added lithium aluminum hydride (1.0M in tetrahydrofuran, 2.1 mL, 2.1 mmol) dropwise. The reaction mixture was stirred at 0°C for 1 hour and quenched successively with water (165 uL), 15% sodium hydroxide solution (165 uL) and water (315 uL). Filtration, solvent evaporation and flash chromatography (silica gel, hexane-ethyl acetate, 85:15-25:75) gave *tert*-butyl-(1S, 3S)-3-hydroxymethyl)cyclopentylcarbamate (**4-2**); ^{1}H NMR (400 MHz, $CDCl_3$,) δ 4.51 (bs, 1H), 3.98 (m, 1H), 3.52 (m, 2H), 2.26 (m, 1H), 2.03 (m, 1H), 1.87 (m, 1H), 1.72 (m, 1H), 1.63-1.56 (m, 1H), 1.44 (s, 9H), 1.41-1.28 (m, 2H).

Tert-butyl-(1S, 3S)-3-iodomethyl)cyclopentylcarbamate **(4-3)**

To a solution of *tert*-butyl-(1S, 3S)-3-hydroxymethyl)cyclopentyl carbamate (**4-2**) (140 mg, 0.65 mmol) in methylene chloride (3 mL), cooled to 0°C was added imidazole (49 mg, 0.72 mmol), triphenylphosphine (189 mg, 0.72 mmol) and iodine (183 mg, 0.72 mmol). The reaction mixture was stirred at 0°C for 1 hour and then stored in the refrigerator overnight. Flash chromatography (silica gel, hexane-ethyl acetate, 100:0-50:50) gave *tert*-butyl-(1S, 3S)-3-

iodomethyl)cyclopentylcarbamate (**4-3**); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.47 (m, 1H), 4.04 (m, 1H), 3.18 (m, 2H), 2.33 (m, 1H), 2.14 (m, 1H), 1.97 (m, 1H), 1.69 (m, 2H), 1.44 (s, 9H), 1.32-1.25 (m, 2H).

SCHEME 5



methyl {1-[(4-methylphenyl)sulfonyl]-1*H*-imidazol-4-yl}acetate (**5-2**)

Through a 0 °C solution of 15g (92 mmol) 4-imidazole acetic acid hydrochloride in 500 mL MeOH was passed HCl gas for 7 minutes. The ice bath was removed and the reaction mixture allowed to stir 16 hours then concentrated to give 15g methyl 4-imidazole acetate hydrochloride as a yellow solid. From this 5.1g (29 mmol) was suspended in 200 mL CH_2Cl_2 and 10 mL (72 mmol) of triethylamine was added causing the reaction mixture to become homogeneous. The reaction mixture was cooled in an ice bath and 6g (32 mmol) p-toluenesulfonylchloride was added. After 15 minutes the ice bath was removed and after 15 more minutes the reaction mixture was diluted with 600 mL CH_2Cl_2 and washed first with a mixture of 300 mL water and 50 mL of 10% aqueous $KHSO_4$, then 300 mL water and finally 300 mL

brine. The CH_2Cl_2 layer was dried over Na_2SO_4, filtered, and concentrated. Purification by automated flash chromatography (120g silica cartridge, linear gradient 20-80% EtOAc/hexane over 20 min, 90 mL/min flow rate.) afforded 7g of methyl {1-[(4-methylphenyl)sulfonyl]-1*H*-imidazol-4-yl}acetate (**5-2**) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, 1H, *J*= 1.47 Hz); 7.83 (d, 2H, *J*= 8.43 Hz); 7.35 (d, 2H, *J*= 8.43 Hz); 7.27 (d, 1H, *J*= 1.1 Hz); 3.71 (s, 3H); 3.61 (s, 2H); 2.44 (s, 3H). Electrospray Mass Spectrum M+H=295.0

dimethyl 2-{1-[(4-methylphenyl)sulfonyl]-1*H*-imidazol-4-yl}malonate(**5-3**)

To a 0 °C solution of 1g (3.4 mmol) methyl {1-[(4-methylphenyl)sulfonyl]-1*H*-imidazol-4-yl}acetate (**5-2**) in 20 mL THF was added 3.7 mL (3.7 mmol, 1M solution in THF) LHMDS and the resulting solution was allowed to stir at 0 °C for 30 min before addition of 0.3 mL (3.74 mmol) methyl cyanoformate. The reaction mixture was allowed to warm to room temperature and quenched after 2 hours with 200 mL saturated aqueous ammonium chloride and extracted with 200 mL EtOAc. The EtOAc layer was washed with 200 mL each of water and brine, dried over Na_2SO_4, filtered and concentrated. Purification by automated flash chromatography (90g silica cartridge, linear gradient 10-90% EtOAc/hexane over 20 min, 70 mL/min flow rate.) afforded 0.6g of dimethyl 2-{1-[(4-methylphenyl)sulfonyl]-1*H*-imidazol-4-yl}malonate (**5-3**) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, 1H, *J*= 1.29 Hz); 7.84 (d, 2H, *J*= 8.42 Hz); 7.51 (d, 1H, *J*= 0.9 Hz); 7.36 (d, 2H, *J*= 8.24 Hz); 4.74 (s, 1H); 3.77 (s, 6H); 2.45 (s, 3H). Electrospray Mass Spectrum M+H=353.0

dimethyl 2-({6-[(*tert*-butoxycarbonyl)amino]pyridin-3-yl}methyl)-2-{1-[(4-methylphenyl)sulfonyl]-1*H*-imidazol-4-yl}malonate(**5-4**)

To a 0 °C solution of 0.9g (2.55 mmol) dimethyl 2-{1-[(4-methylphenyl)sulfonyl]-1*H*-imidazol-4-yl}malonate (**5-3**) in 10 mL DMF was added 0.1g (2.55 mmol, 60% dispersion in mineral oil) sodium hydride. The reaction mixture was allowed to stir 15 minutes at 0°C then warmed to room temperature for 1 hour then recooled to 0°C whereupon 0.73g (2.55 mmol) *tert*-butyl 5-(bromomethyl)-pyridin-2-ylcarbamate (**1-4**) was added as a solid in one portion. After stirring 30 minutes at 0°C the reaction was quenched with 300 mL water and extracted with 300 mL CH_2Cl_2 and 2x200 mL EtOAc. The organic extracts were dried over Na_2SO_4, filtered and concentrated. Purification by automated flash chromatography (120g

silica cartridge, linear gradient 10-70% EtOAc/hexane over 20 min, 90 mL/min flow rate.) afforded dimethyl 2-({6-[(*tert*-butoxycarbonyl)amino]pyridin-3-yl}methyl)-2-{1-[(4-methylphenyl)sulfonyl]-1*H*-imidazol-4-yl}malonate(**5-4**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, 1H, *J*= 1.29 Hz); 7.77 (d, 2H, *J*= 8.42 Hz); 7.66 (d, 1H, *J*= 2.39 Hz); 7.52 (m, 2H); 7.46 (d, 1H, *J*= 8.61 Hz); 7.41 (d, 2H, *J*= 8.34 Hz); 6.61 (dd, 1H, *J*= 8.60 and 2.19 Hz); 3.74 (s, 6H); 3.50 (s, 2H); 2.49 (s, 3H); 1.53 (s, 9H). Electrospray Mass Spectrum M+H=559.2

3-(6-aminopyridin-3-yl)-2-(1*H*-imidazol-4-yl)propanoic acid (**5-5**)

To a suspension of 0.075g (0.13 mmol) dimethyl 2-({6-[(*tert*-butoxycarbonyl)amino] pyridin-3-yl}methyl)-2-{1-[(4-methylphenyl)sulfonyl]-1*H*-imidazol-4-yl}malonate(**5-4**) in 1 mL water was added 1 mL concentrated HCl and the resulting solution heated to 95 °C for 8 hours, cooled, and concentrated. Purification by ion exchange (1g Varian SCX cartridge, load in 1:1 acetonitrile : water, rinse with 10 mL acetonitrile, elute with 2 mL NH_3/MeOH.) followed by lyophilization from 1 mL water afforded 0.03g 3-(6-aminopyridin-3-yl)-2-(1*H*-imidazol-4-yl)propanoate (**5-5**) as a free base ^{1}H NMR (400 MHz, $DMSOd_6$) δ 7.64 (d, 1H, *J*=1.83 Hz);7.47 (s, 1H); 7.13 (dd, 1H, *J*=8.42 and 2.38 Hz); 6.74 (s, 1H); 6.29 (d, 1H, *J*=8.25 Hz); 5.6 (m, 1H); 3.57 (t, 1H, *J*=7.69 Hz); 2.95 (dd, 1H, *J*=13.7 and 8.06 Hz); 2.78 (dd, 1H, *J*=13.7 and 7.14 Hz).

methyl (1-trityl-1*H*-imidazol-4-yl)acetate (**5-6**)

To a solution of 9g (51 mmol) methyl 4-imidazole acetate hydrochloride in 100 mL DMF was added 15 mL (107 mmol) triethylamine causing a precipitate to form. To this mixture was added 15.6g (51 mmol) trityl chloride and the thick mixture was stirred vigorously for 16 hours then concentrated to 1/5 volume. The resulting paste was partitioned between 1200 mL EtOAc and 800 mL water adjusted to pH=9 with 50 mL saturated sodium bicarbonate solution. The organic layer was washed with 800 mL each of water and brine, dried over Na_2SO_4, filtered and concentrated to provide 20g of methyl (1-trityl-1*H*-imidazol-4-yl)acetate (**5-6**) as a tan solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, 1H, *J*= 1.37 Hz); 7.33 (m, 9H) 7.14 (m, 6H); 6.77 (br s, 1H);3.70 (s, 3H); 3.62 (s, 2H);

dimethyl 2-(1-trityl-1*H*-imidazol-4-yl)malonate (**5-7**)

To a 0 °C solution of 5g (13 mmol) methyl (1-trityl-1*H*-imidazol-4-yl)acetate (**5-6**) in 100 mL THF was added 7.2 mL (14.4 mmol, 2M solution) lithium diisopropylamide and the reaction mixture was allowed to stir 2 hours at 0 °C before 1 mL(13 mmol) methyl cyanoformate was added. After 1 hour at 0 °C the reaction mixture was quenched with 200 mL saturated aqueous ammonium chloride and extracted with 200 mL EtOAc. The EtOAc layer was washed with saturated sodium bicarbonate solution and brine, dried over Na_2SO_4, filtered, and concentrated. Purification by automated flash chromatography (120g silica cartridge, linear gradient 20-100% EtOAc/hexane over 20 min, 90 mL/min flow rate.) followed by repurification of mixed fractions (as above) afforded 3.5g dimethyl 2-(1-trityl-1*H*-imidazol-4-yl)malonate (**5-7**) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, 1H, *J*= 1.46 Hz); 7.33 (m, 9H) 7.14 (m, 6H); 6.99 (d, 1H, *J*= 1.46 Hz);4.79 (s, 1H); 3.75 (s, 6H)

dimethyl 2-({6-[(*tert*-butoxycarbonyl)amino]pyridin-3-yl}methyl)-2-(1-trityl-1*H*-imidazol-4-yl)malonate (**5-8**)

To a 0 °C solution of 0.4g (0.9 mmol) dimethyl 2-(1-trityl-1*H*-imidazol-4-yl)malonate (**5-7**) in 25 mL DMF was 0.04g (1.1 mmol, 60% dispersion in oil) NaH and the resulting mixture was warmed to room temperature for 1 hour then cooled to 0 °C before addition of *tert*-butyl 5-(bromomethyl)-pyridin-2-ylcarbamate as a solid in one portion. After 1 hour at 0 °C the reaction mixture was diluted with 300 mL EtOAc, washed with 200 mL each of saturated sodium bicarbonate solution, water, and brine, dried over Na_2SO_4, filtered and concentrated. Purification by automated flash chromatography (40g silica cartridge, linear gradient 30-100% EtOAc/hexane over 20 min, 40 mL/min flow rate.) provided 0.56g dimethyl 2-({6-[(*tert*-butoxycarbonyl)amino]pyridin-3-yl}methyl)-2-(1-trityl-1*H*-imidazol-4-yl)malonate (**5-8**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (m, 2H); 7.43 (d, 1H, *J*= 1.28 Hz); 7.31 (m, 10H) 7.08 (m, 6H); 7.04 (d, 1H, *J*= 1.28 Hz); 3.72 (s, 6H); 3.62 (s, 2H); 1.54 (s, 9H). electrospray mass spectrum M+H=647.2

dimethyl 2-[(6-aminopyridin-3-yl)methyl]-2-(1*H*-imidazol-4-yl)malonate (**5-9**)

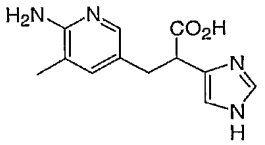
To a 0 °C solution of 0.28g (0.43 mmol) dimethyl 2-({6-[(*tert*-butoxycarbonyl)amino]pyridin-3-yl}methyl)-2-(1-trityl-1*H*-imidazol-4-yl)malonate (**5-8**) in 0.5 mL CH_2Cl_2 was added 0.14 mL (0.87 mmol) triethylsilane and 3 mL TFA. The reaction mixture was allowed to stir 1 h at 0 °C then warmed to room temperature for 3 hours, then 5 mL toluene was added and the mixture concentrated.

Purification by automated flash chromatography (40g silica cartridge, linear gradient 2-20% MeOH(10% NH_4OH)/ CH_2Cl_2 over 20 min, 40 mL/min flow rate.) provided 0.05g dimethyl 2-[(6-aminopyridin-3-yl)methyl]-2-(1*H*-imidazol-4-yl)malonate (**5-9**) ^1H NMR (400 MHz, $DMSOd_6$) δ 11.9 (s, 1H); 7.62 (s, 1H); 7.21 (d, 1H, *J*= 2.01 Hz); 7.04 (s, 1H); 6.59 (dd, 1H, *J*=2.38 and 8.60 Hz); 6.16 (d, 1H, *J*=8.43 Hz); 5.64 (s, 2H); 3.62 (s, 6H); 3.30 (s, 2H). electrospray mass spectrum M+H= 305.1

3-(6-aminopyridin-3-yl)-2-(1*H*-imidazol-4-yl)propanoic acid (**5-5**)

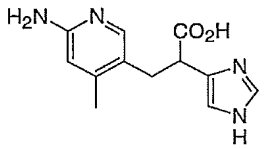
To a suspension of 0.05g (0.15 mmol) dimethyl 2-[(6-aminopyridin-3-yl)methyl]-2-(1*H*-imidazol-4-yl)malonate (**5-9**) in 4 mL water was added 4 mL concentrated HCl and the resulting solution heated to 80 °C for 8 hours, cooled and concentrated. Added 4 mL water twice and concentrated, added 4 mL CH_2Cl_2 and concentrated to give 3-(6-aminopyridin-3-yl)-2-(1*H*-imidazol-4-yl)propanoate dihydrochloride (**5-5**) as a hygroscopic foam. ^1H NMR (400 MHz, $DMSOd_6$) δ 9.00 (s, 1H); 7.91 (br s, 2H); 7.73 (m, 2H); 7.52 (s, 1H); 6.88 (d, 1H, *J*=9.71 Hz); 4.16 (t, 1H, *J*=8.79 Hz); 3.20 (dd, 1H, *J*=13.9 and 6.23 Hz); 3.06 (dd, 1H, *J*=13.9 and 8.97 Hz); High resolution mass spectrum FT/ICR calculated M+H=233.1033, found 233.1031.

3-(6-amino-5-methylpyridin-3-yl)-2-(1H-imidazol-4-yl)propanoic acid (**5-10**)



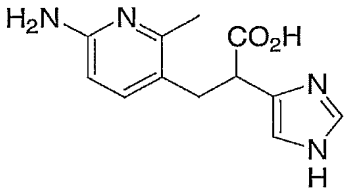
3-(6-amino-5-methylpyridin-3-yl)-2-(1H-imidazol-4-yl)propanoic acid (**5-10**) was prepared from tert-butyl 5-(bromomethyl)-3-methylpyridin-2-ylcarbamate (**2-5**) and dimethyl 2-(1-trityl-1H-imidazol-4-yl)malonate (**5-7**) using a similar procedure as described for the preparation of (**5-5**).
Electrospray Mass Spectrum M+H=247.6.

3-(6-amino-4-methylpyridin-3-yl)-2-(1H-imidazol-4-yl)propanoic acid (**5-11**)



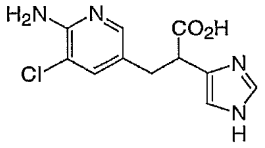
3-(6-amino-4-methylpyridin-3-yl)-2-(1H-imidazol-4-yl)propanoic acid (**5-11**) was prepared from tert-butyl 5-(bromomethyl)-4-methylpyridin-2-ylcarbamate (prepared from 5-bromo-4-methylpyridin-2-amine using a similar procedure as described for the preparation of (**2-5**)) and dimethyl 2-(1-trityl-1H-imidazol-4-yl)malonate (**5-7**) using a similar procedure as described for the preparation of (**5-5**). Electrospray Mass Spectrum M+H=247.6.

3-(6-amino-2-methylpyridin-3-yl)-2-(1H-imidazol-4-yl)propanoic acid (**5-12**)



3-(6-amino-2-methylpyridin-3-yl)-2-(1H-imidazol-4-yl)propanoic acid (**5-12**) was prepared from tert-butyl 3-(bromomethyl)-2-methylpyridin-6-ylcarbamate (prepared from 3-bromo-2-methylpyridin-6-amine using a similar procedure as described for the preparation of (**2-5**)) and dimethyl 2-(1-trityl-1H-imidazol-4-yl)malonate (**5-7**) using a similar procedure as described for the preparation of (**5-5**). Electrospray Mass Spectrum M+H=247.6.

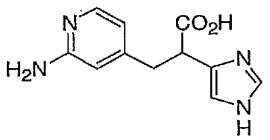
3-(6-amino-5-chloropyridin-3-yl)-2-(1H-imidazol-4-yl)propanoic acid (**5-13**)



3-(6-amino-5-chloropyridin-3-yl)-2-(1H-imidazol-4-yl)propanoic acid (**5-13** was prepared by chlorination of dimethyl 2-[(6-aminopyridin-3-yl)methyl]-2-(1H-imidazol-4-yl)malonate (**5-9**) using NCS and final hydrolysis/decarboxylation as described for the preparation of (**5-5**).

Electrospray Mass Spectrum M+H=267.6.

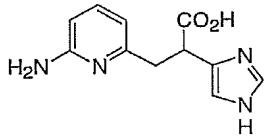
3-(2-aminopyridin-4-yl)-2-(1H-imidazol-4-yl)propanoic acid (**5-14**)



3-(2-aminopyridin-4-yl)-2-(1H-imidazol-4-yl)propanoic acid (**5-14**) was prepared from tert-butyl 4-(bromomethyl)pyridin-2-ylcarbamate (**3-2**) and dimethyl 2-(1-trityl-1H-imidazol-4-yl)malonate (**5-7**) using a similar procedure as described for the preparation of (**5-5**).

Electrospray Mass Spectrum M+H=233.1.

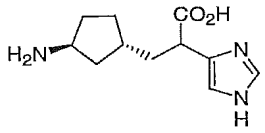
3-(6-aminopyridin-2-yl)-2-(1H-imidazol-4-yl)propanoic acid (**5-15**)



3-(6-aminopyridin-2-yl)-2-(1H-imidazol-4-yl)propanoic acid (**5-15**) was prepared from tert-butyl 2-(bromomethyl)pyridin-6-ylcarbamate (prepared from tert-butyl 2-methyl-pyridin-6-ylcarbamate using a procedure similar as described in Scheme3) and dimethyl 2-(1-trityl-1H-imidazol-4-yl)malonate (**5-7**) using a similar procedure as described for the preparation of (**5-5**).

Electrospray Mass Spectrum M+H=233.6

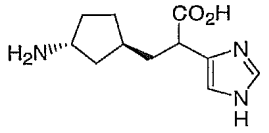
3-[(1R,3S)-3-aminocyclopentyl]-2-(1H-imidazol-4-yl)propanoic acid (**5-16**)



3-[(1R,3S)-3-aminocyclopentyl]-2-(1H-imidazol-4-yl)propanoic acid (**5-16**) was prepared from *tert*-butyl-(1S, 3S)-3-iodomethyl)cyclopentylcarbamate (**4-**

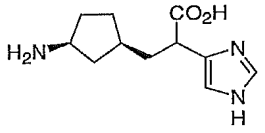
3) and dimethyl 2-({1-[(4-methylphenyl)sulfonyl]-1H-imidazol-4-yl}methyl)malonate (**5-3**) using a similar procedure as described for the preparation of (**5-5**).
Electrospray Mass Spectrum M+H=224.6.

3-[(1S,3R)-3-aminocyclopentyl]-2-(1H-imidazol-4-yl)propanoic acid (**5-17**)



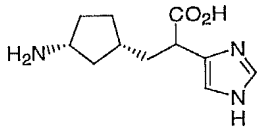
3-[(1S,3R)-3-aminocyclopentyl]-2-(1H-imidazol-4-yl)propanoic acid (**5-17**) was prepared from *tert*-butyl-(1R, 3R)-3-iodomethyl)cyclopentylcarbamate and dimethyl 2-({1-[(4-methylphenyl)sulfonyl]-1H-imidazol-4-yl}methyl)malonate (**5-3**) using a similar procedure as described for the preparation of (**5-5**).
Electrospray Mass Spectrum M+H=224.6.

3-[(1S,3S)-3-aminocyclopentyl]-2-(1H-imidazol-4-yl)propanoic acid (**5-18**)



3-[(1S,3S)-3-aminocyclopentyl]-2-(1H-imidazol-4-yl)propanoic acid (**5-18**) was prepared from *tert*-butyl-(1R, 3S)-3-iodomethyl)cyclopentylcarbamate and dimethyl 2-({1-[(4-methylphenyl)sulfonyl]-1H-imidazol-4-yl}methyl)malonate (**5-3**) using a similar procedure as described for the preparation of (**5-5**).
Electrospray Mass Spectrum M+H=224.6.

3-[(1R,3R)-3-aminocyclopentyl]-2-(1H-imidazol-4-yl)propanoic acid (**5-19**)

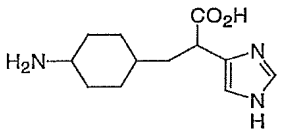


3-[(1R,3R)-3-aminocyclopentyl]-2-(1H-imidazol-4-yl)propanoic acid (**5-19**) was prepared from *tert*-butyl-(1S, 3R)-3-iodomethyl)cyclopentylcarbamate and

dimethyl 2-({1-[(4-methylphenyl)sulfonyl]-1H-imidazol-4-yl}methyl)malonate (**5-3**) using a similar procedure as described for the preparation of (**5-5**).
Electrospray Mass Spectrum M+H=224.6.

5

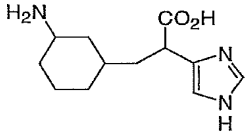
3-(4-aminocyclohexyl)-2-(1H-imidazol-4-yl)propanoic acid (**5-20**)



3-(4-aminocyclohexyl)-2-(1H-imidazol-4-yl)propanoic acid (**5-20**) was
10 prepared from tert-butyl 4-(iodomethyl)cyclohexylcarbamate (derived from the corresponding amino-acid similarly as described in scheme 4) and dimethyl 2-({1-[(4-methylphenyl)sulfonyl]-1H-imidazol-4-yl}methyl)malonate (**5-3**) using a similar procedure as described for the preparation of (**5-5**).
Electrospray Mass Spectrum M+H=238.6.

15

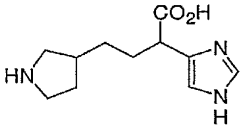
3-(3-aminocyclohexyl)-2-(1H-imidazol-4-yl)propanoic acid (**5-21**)



3-(3-aminocyclohexyl)-2-(1H-imidazol-4-yl)propanoic acid (**5-21**) was
20 prepared from tert-butyl 3-(iodomethyl)cyclohexylcarbamate (derived from the corresponding amino-acid similarly as described in scheme 4) and dimethyl 2-({1-[(4-methylphenyl)sulfonyl]-1H-imidazol-4-yl}methyl)malonate (**5-3**) using a similar procedure as described for the preparation of (**5-5**).
Electrospray Mass Spectrum M+H=238.6.

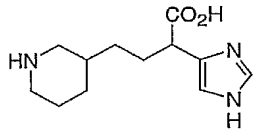
25

2-(1H-imidazol-4-yl)-4-pyrrolidin-3-ylbutanoic acid (**5-22**)



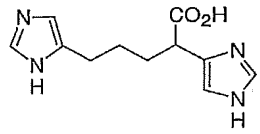
2-(1H-imidazol-4-yl)-4-pyrrolidin-3-ylbutanoic acid (**5-22**) was prepared from tert-butyl 3-(2-iodoethyl)pyrrolidine-1-carboxylate (derived from the corresponding amino-acid similarly as described in scheme 4) and dimethyl 2-({1-[(4-methylphenyl)sulfonyl]-1H-imidazol-4-yl}methyl)malonate (**5-3**) using a similar procedure as described for the preparation of (**5-5**).
Electrospray Mass Spectrum M+H=224.6.

2-(1H-imidazol-4-yl)-4-piperidin-3-ylbutanoic acid (**5-23**)



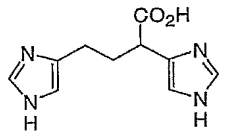
2-(1H-imidazol-4-yl)-4-piperidin-3-ylbutanoic acid (**5-23**) was prepared from tert-butyl 3-(2-iodoethyl)piperidine-1-carboxylate (derived from the corresponding amino-acid similarly as described in scheme 4) and dimethyl 2-({1-[(4-methylphenyl)sulfonyl]-1H-imidazol-4-yl}methyl)malonate (**5-3**) using a similar procedure as described for the preparation of (**5-5**).
Electrospray Mass Spectrum M+H=238.6.

2-(1H-imidazol-4-yl)-5-(1H-imidazol-5-yl)pentanoic acid (**5-24**)



2-(1H-imidazol-4-yl)-5-(1H-imidazol-5-yl)pentanoic acid (**5-24**) was prepared from 4-(3-iodopropyl)-N,N-dimethyl-1H-imidazole-1-sulfonamide (derived from methyl 3-{1-[(dimethylamino)sulfonyl]-1H-imidazol-4-yl}propanoate similarly as described in scheme 4) and dimethyl 2-({1-[(4-methylphenyl)sulfonyl]-1H-imidazol-4-yl}methyl)malonate (**5-3**) using a similar procedure as described for the preparation of (**5-5**).
Electrospray Mass Spectrum M+H=235.6.

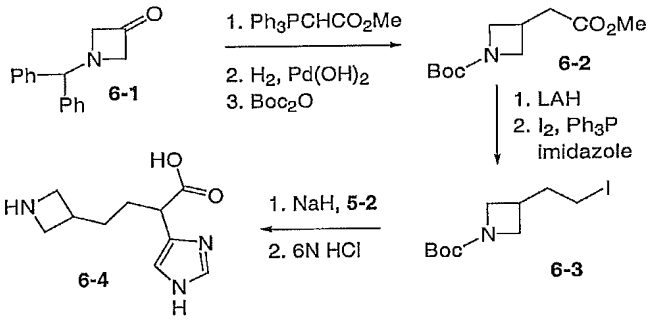
2-(1H-imidazol-4-yl)-5-(1H-imidazol-5-yl)butanoic acid (**5-25**)



2-(1H-imidazol-4-yl)-5-(1H-imidazol-5-yl)butanoic acid (**5-25**) was prepared from 4-(2-iodoethyl)-N,N-dimethyl-1H-imidazole-1-sulfonamide (derived from methyl 2-{1-[(dimethylamino)sulfonyl]-1H-imidazol-4-yl}acetate similarly as described in scheme 4) and dimethyl 2-({1-[(4-methylphenyl)sulfonyl]-1H-imidazol-4-yl}methyl)malonate (**5-3**) using a similar procedure as described for the preparation of (**5-5**).

Electrospray Mass Spectrum M+H=221.1.

SCHEME 6



tert-butyl 3-(2-methoxy-2-oxoethyl)azetidine-1-carboxylate (**6-2**)

To a solution of 1-benzhydrylazetidin-3-oxo (500 mg, 2.107 mmol) in dichloroethane (5 mL) is added methyl-(triphenylphosphoranylidene)-acetate (775 mg, 2.32 mmol) and the mixture is stirred at 115 °C in a sealed tube for 1 h 25. The reaction mixture is allowed to cool to room temperature, concentrated in vacuo and purified by flash chromatography (silica gel, hexane to 25% EtOAc in hexane) to give methyl (1-benzhydrylazetidin-3-ylidene)acetate (590 mg) as a thick oil.

A solution of methyl (1-benzhydrylazetidin-3-ylidene)acetate (408 mg, 1.39 mmol) and 1N HCl (1.53 mL, 1.53 mmol) in MeOH (25 mL) is degassed with argon and $Pd(OH)_2$ (400 mg, 20%, wet) is added. The reaction mixture is vigorously stirred at 60 °C under 1 atm H_2 for 2 h 25. The reaction mixture is allowed to cool to room

temperature, filtered on cellite and concentrated in vacuo. The residue is taken in dichloromethane (25 mL), Et_3N (0.29 mL, 2.09 mmol) and ditertbutyldicarbonate (395 mg, 1.81 mmol) are added. The reaction mixture is stirred at room temperature for 1 h, concentrated in vacuo and purified by flash chromatography (silica gel, 10% to 25% EtOAc in hexane) to give tert-butyl 3-(2-methoxy-2-oxoethyl)azetidine-1-carboxylate (**6-2**) (250 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.09 (t, 2H, *J*=8.5 Hz); 3.68 (s, 3 H); 3.60 (dd, 2H, *J*=8.5, 5.5 Hz); 2.94-2.82 (m, 1 H); 2.73 (d, 2H, *J*=7.91 Hz); 1.42 (s, 9 H).

tert-butyl 3-(2-iodoethyl)azetidine-1-carboxylate (**6-3**)

To solution of tert-butyl 3-(2-methoxy-2-oxoethyl)azetidine-1-carboxylate (**6-2**) (250 mg, 1.09 mmol) in THF (10 mL) cooled to 0 °C is added LAH (1.74 mL, 1.74 mmol, 1M in diethyl ether) slowly. After 15 min stirring at 0 °C, the reaction mixture is added to a vigorously stirred mixture of diethyl ether and aqueous sodium potassium tartrate. The mixture is vigorously stirred at room temperature for 15 min, the organic layer is separated and the aqueous layer back extracted with EtOAc . The combined organic layer is dried over magnesium sulfate, concentrated in vacuo and purified by flash chromatography (silica gel, 50% to 100% EtOAc in hexane) to give tert-butyl 3-(2-hydroxyethyl)azetidine-1-carboxylate (200 mg). Electrospray mass spectrum M+Na=224.6.

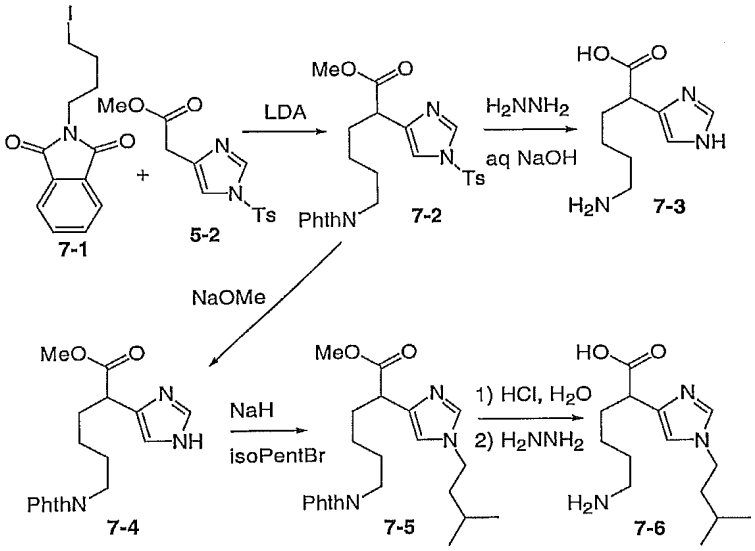
To a solution of tert-butyl 3-(2-hydroxyethyl)azetidine-1-carboxylate (100 mg, 0.5 mmol) in dichloromethane (5 mL) cooled to 0 °C is added imidazole (40.6 mg, 0.60 mmol), iodine (139 mg, 0.55 mmol) and triphenylphosphine (163 mg, 0.62 mmol) and the ice bath is removed after 1 min. The reaction mixture is stirred at room temperature for 3 h 30, filtered on a silica gel pad eluting with 25% EtOAc in hexane, concentrated in vacuo and purified by flash chromatography (silica gel, 0% to 30% EtOAc in hexane) to give tert-butyl 3-(2-iodoethyl)azetidine-1-carboxylate (**6-3**) (138 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.4 (t, 2H, *J*=8.5 Hz); 3.57 (dd, 2H, *J*=8.5, 5.9 Hz); 3.1 (t, 2H, *J*=6.8 Hz); 2.7-2.58 (m, 1 H); 2.15 (q, 2H, *J*=6.8 Hz); 1.42 (s, 9 H).
Electrospray mass spectrum M+H=312.5.

4-azetidin-3-yl-2-{1-[(4-methylphenyl)sulfonyl]-1H-imidazol-4-yl}butanoic acid (**6-4**)

To a solution of methyl {1-[(4-methylphenyl)sulfonyl]-1*H*-imidazol-4-yl}acetate (**6-3**) (250 mg, 0.85 mmol) in THF (3 mL) cooled to 0 °C is added LiHMDS (0.85 mL, 0.85 mL, 1 M in THF). The reaction mixture is stirred at 0 °C for 15 min and tert-butyl 3-(2-iodoethyl)azetidine-1-carboxylate (120 mg, 0.39 mmol) in THF (2 mL) is added. The reaction mixture is stirred at room temperature for 30 min and at 50 °C for 25 min. The reaction mixture is diluted with EtOAc, washed with aqueous NH_4Cl, water and brine, dried over sodium sulfate, concentrated in vacuo and purified by flash chromatography (silica gel, 30% to 70% EtOAc in hexane) to give tert-butyl 3-(4-methoxy-3-{1-[(4-methylphenyl)sulfonyl]-1H-imidazol-4-yl}-4-oxobutyl)azetidine-1-carboxylate containing ca. 20% dialkylated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, 1 H, *J*=1.8 Hz); 7.82 (d, 2 H, *J*=8.4 Hz); 7.36 (d, 2 H, *J*=8.4 Hz); 7.19 (br s, 1 H); 3.95 (t, 2H, *J*=8.4 Hz); 3.95-3.86 (m, 1 H); 3.69 (s, 3 H); 3.52-3.43 (m, 2 H); 2.5 (s, 3 H); 2.44-2.38 (m, 1 H); 1.95-1.7 (m, 2 H); 1.58-1.47 (m, 2 H); 1.42 (s, 9 H).
Electrospray mass spectrum M+H=478.6.

Tert-butyl 3-(4-methoxy-3-{1-[(4-methylphenyl)sulfonyl]-1H-imidazol-4-yl}-4-oxobutyl)azetidine-1-carboxylate (45 mg, 0.09 mmol) was taken in 6N HCl (5 mL) and heated at 105 °C for 1h30. The reaction mixture was concentrated in vacuo and purified by preparative reverse phase HPLC (20x150 mm C18 column, 0-95% AcN/H_2O (0.1%TFA) over 25 minutes) to give 4-azetidin-3-yl-2-{1-[(4-methylphenyl)sulfonyl]-1H-imidazol-4-yl}butanoic acid bis-TFA salt (**6-4**). ^{1}H NMR (400 MHz, CD_3OD) δ 8.9 (s, 1 H); 7.5 (s, 1 H); 4.93 (br t, 2 H, *J*=9.6 Hz); 3.9 (t, 1 H, *J*=7.8 Hz); 3.78 (br t, 2 H, *J*=9.6 Hz); 3.02-2.87 (m, 1 H); 2.12-1.96 (m, 1 H); 1.90-1.60 (m, 2 H).
Electrospray mass spectrum M+H=210.6.

SCHEME 7



Methyl 6-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-2-{1-[(4-methylphenyl)sulfonyl]-1*H*-imidazol-4-yl}hexanoate (**7-2**)

To a 0 °C solution of 0.16 mL (1.12 mmol) diisopropylamine in 2 mL THF was added 0.45 mL (1.12 mmol, 2.5M solution in hexane) butyllithium and the reaction mixture was allowed to stir 5 minutes at 0 °C before transferring this mixture via cannula to a 0°C solution of 0.3g (1.0 mmol) methyl {1-[(4-methylphenyl)sulfonyl]-1*H*-imidazol-4-yl}acetate (**5-2**) in 3 mL THF. After 15 minutes a 0 °C, 0.35g (1.07 mmol) 1-iodo-4-phthalimidobutane was added as a solid and the reaction mixture was allowed to warm slowly to room temperature over 3 hours, then diluted with 200 mL EtOAc and washed with 200 mL each of saturated aqueous ammonium chloride, water, and brine, then dried over Na_2SO_4, filtered and concentrated. Purification by automated flash chromatography (40g silica cartridge, 2% acetone/ CH_2Cl_2 for 15 min then ramp up to 80% acetone/ CH_2Cl_2 over 5 min, 40 mL/min flow rate.) afforded methyl 6-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-2-{1-[(4-methylphenyl)sulfonyl]-1*H*-imidazol-4-yl}hexanoate (**7-2**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, 1H, *J*=1.28 Hz); 7.83 (m, 4H); 7.71 (m, 2H); 7.36 (d, 2H, *J*=8.06 Hz); 7.20 (br s, 1H); 3.67 (3, 3H); 3.61 (m, 3H); 2.45 (s, 3H); 1.97 (m, 1H); 1.90 (m, 1H); 1.67 (m, 2H); 1.31 (m, 2H). electrospray mass spectrum M+H=496.1

6-amino-2-(1*H*-imidazol-4-yl)hexanoic acid (**7-3**)

To a solution of 0.009g (0.018 mmol) methyl 6-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-2-{1-[(4-methylphenyl)sulfonyl]-1*H*-imidazol-4-yl}hexanoate (**7-2**) in 1 mL methanol was added 3 uL (0.1 mmol) hydrazine and the reaction mixture was stirred at room temperature for 3 days, then 0.18 mL (0.18mmol, 1M solution in water) NaOH was added and the reaction mixture stirred an additional 2 days then reduced to 0.3 mL. Purification by preparative reverse phase HPLC (20x150 mm C18 column, 0-95% AcN/H_2O (0.1%TFA) over 25 minutes) to provided 6-amino-2-(1*H*-imidazol-4-yl)hexanoic acid, ditrifluoroacetate salt (**7-3**) . ^{1}H NMR (400 MHz, DMSO d_6) δ 8.87 (d, 1H, *J*=1.28 Hz); 7.49 (d, 1H, *J*=0.82 Hz); 3.90 (t, 1H, *J*=7.60 Hz); 2.92 (t, 2H, *J*=7.69 Hz); 2.14 (m, 1H); 1.96 (m, 1H); 1.70 (quint, 2H, *J*=7.69 Hz); 1.45 (m, 2H). electrospray mass spectrum M+H=198.1

methyl 6-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-2-(1*H*-imidazol-4-yl)hexanoate (**7-4**)

To a solution of 0.84g (1.7 mmol) methyl 6-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-2-{1-[(4-methylphenyl)sulfonyl]-1*H*-imidazol-4-yl}hexanoate (**7-2**) in 10 mL MeOH was added 0.04 mL (0.02 mmol, 0.5M solution in MeOH) NaOMe and the resulting mixture allowed to stir 5 hours, then 0.08 mL (0.04 mmol, 0.5M solution in MeOH) more NaOMe was added and the mixture allowed to stir 18 hours. The reaction was quenched by addition of 0.34 mL (3.4 mol) piperidine was added and after 30 minutes the mixture was diluted with 200 mL EtOAc, washed with 200 mL water, saturated aqueous $NaHCO_3$ solution, and brine, dried over Na_2SO_4, filtered, and concentrated. Purification by automated flash chromatography (40g cartridge, linear gradient 0-10% MeOH/CH_2CL_2 over 20 minutes) afforded 0.6g methyl 6-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-2-(1*H*-imidazol-4-yl)hexanoate (**7-4**).). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (m, 2H); 7.71 (m, 2H); 7.57 (s, 1H); 6.92 (s, 1H); 3.7 (m, 6H); 2.08-1.87 (m, 2H); 1.70 (m, 2H); 1.35 (m, 2H).Electrospray Mass Spectrum (M+H) = 342.1.

Methyl 6-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-2-(1-isopentyl-1*H*-imidazol-4-yl)hexanoate (**7-5**)

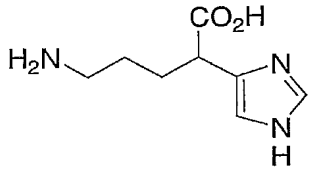
To a 0 °C solution of 0.3g (0.9 mmol) methyl 6-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-2-(1*H*-imidazol-4-yl)hexanoate (**7-4**) in 1 mL DMF was added 0.04g (0.9 mmol, 60% disp. in oil) NaH and the mixture was allowed to warm to room temperature and stir 1 hr before adding 0.11 mL (0.9 mmol) isopentyl

bromide. After 2 hours the mixture was diluted with 100 mL EtOAc, washed with 100 mL each of aqueous $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and concentrated. Purification by automated flash chromatography (40g cartridge, linear gradient 0-10% MeOH/CH_2CL_2 over 20 minutes) afforded 0.11g methyl 6-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-2-(1-isopentyl-1*H*-imidazol-4-yl)hexanoate (**7-5**).). ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (m, 2H); 7.70 (m, 2H); 7.34 (s, 1H); 6.80 (s, 1H); 3.87 (t, 2H, *J*=7.42 Hz);3.67 (m, 6H); 2.05-1.89 (m, 2H); 1.70 (m, 5H); 1.36 (m, 2H); 0.94 (d, 6H. *J*=6.5 Hz). Electrospray Mass Spectrum (M+H) = 412.1

6-amino-2-(1-isopentyl-1*H*-imidazol-4-yl)hexanoic acid (**7-6**)

To a suspension of 0.1g (0.24 mmol) methyl 6-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-2-(1-isopentyl-1*H*-imidazol-4-yl)hexanoate (**7-5**) in 3 mL water was added 3 mL 12N HCl and the mixture heated to 100 °C for 45 minutes, then the mixture was cooled and concentrated. Twice, the residue was dissolved in 10 mL water and concentrated then it was dissolved in 2 mL water and 0.16 mL (5 mmol) hydrazine was added and the mixture was allowed to stir 2 hours at room temperature. Twice, the residue was dissolved in 10 mL water and concentrated. Purification by preparative reverse phase HPLC (two injections, 20x150 mm C18 column, 0-95% AcN/H_2O (0.1%TFA) over 25 minutes) followed by lyophilization from water provided 0.085g 6-amino-2-(1-isopentyl-1*H*-imidazol-4-yl)hexanoic acid (**7-6**) as its trifluoroacetate salt. ^1H NMR (400 MHz, DMSO d_6) δ 9.08 (s, 1H); 7.68 (br s, 3H); 4.16 (t, 2H, *J*=7.69 Hz); 3.76 (t, 1H, *J*=7.51 Hz); 2.76 (m, 2H); 1.98 (m, 1H); 1.81 (m, 1H); 1.70 (q, 2H, *J*=7.14 Hz); 1.53 (m, 2H); 1.28 (m, 2H); 0.91 (d, 6H, *J*=6.59 Hz). Electrospray mass spectrum M+H=268.1

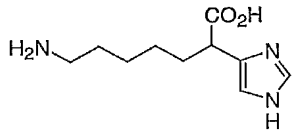
5-amino-2-(1*H*-imidazol-4-yl)pentanoic acid (**7-7**)



5-amino-2-(1*H*-imidazol-4-yl)pentanoic acid (**7-7**) was prepared from 1-iodo-3-pthalimidopropane and methyl {1-[(4-methylphenyl)sulfonyl]-1*H*-imidazol-4-yl}acetate (**5-2**) using a similar procedure as described for the preparation of (**7-3**).

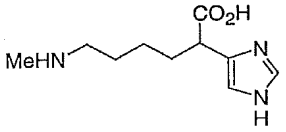
Electrospray Mass Spectrum M+H=184.5.

7-amino-2-(1*H*-imidazol-4-yl)heptanoic acid (**7-8**)



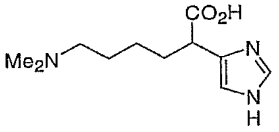
7-amino-2-(1*H*-imidazol-4-yl)heptanoic acid (**7-8**) was prepared from 1-iodo-5-pthalimidopentane and methyl {1-[(4-methylphenyl)sulfonyl]-1*H*-imidazol-4-yl}acetate (**5-2**) using a similar procedure as described for the preparation of (**7-3**).
Electrospray Mass Spectrum M+H=212.0

6-methylamino-2-(1*H*-imidazol-4-yl)hexanoic acid (**7-9**)



6-methylamino-2-(1*H*-imidazol-4-yl)hexanoic acid (**7-9**) was prepared from tert-butyl 4-iodobutyl(methyl)carbamate and dimethyl 2-({1-[(4-methylphenyl)sulfonyl]-1H-imidazol-4-yl}methyl)malonate (**5-3**) using a similar procedure as described for the preparation of (**5-5**).
Electrospray Mass Spectrum M+H=212.6

6-dimethylamino-2-(1*H*-imidazol-4-yl)hexanoic acid (**7-10**)

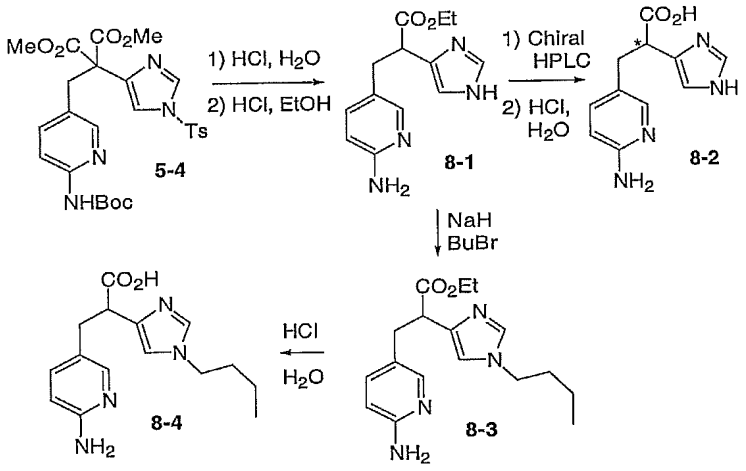


6-dimethylamino-2-(1*H*-imidazol-4-yl)hexanoic acid (**7-10**) was prepared from dimethyl 2-(4-aminobutyl)-2-{1-[(4-methylphenyl)sulfonyl]-1H-imidazol-4-yl}malonate (prepared from 1-iodo-4-pthalimidobutane and dimethyl 2-({1-[(4-methylphenyl)sulfonyl]-1H-imidazol-4-yl}methyl)malonate (**5-3**), followed by phthalimide removal with hydrazine) by dimethylation with formaldehyde and sodium

triacetoxyborohydride and final deprotection as described in the conversion of (**5-4**) to (**5-5**).

Electrospray Mass Spectrum M+H=226.6.

SCHEME 8



ethyl 3-(6-aminopyridin-3-yl)-2-(1*H*-imidazol-4-yl)propanoate (**8-1**)

To a suspension of 0.57g (1 mmol) dimethyl 2-({6-[(*tert*-butoxycarbonyl)amino]pyridin-3-yl}methyl)-2-{1-[(4-methylphenyl)sulfonyl]-1*H*-imidazol-4-yl}malonate (**5-4**) in 7 mL water was added 5 mL (61 mmol, 12M solution in water) concentrated HCl. The resulting solution was heated to 100 °C for 8 hours, cooled, and concentrated to give 3-(6-aminopyridin-3-yl)-2-(1*H*-imidazol-4-yl)propanoate (**5-5**). The resulting residue was twice dissolved in 15 mL absolute ethanol and concentrated leaving a foam that was dissolved in 10 mL absolute ethanol. To this was added 3 mL (3 mmol, 1M solution in diethyl ether) HCl and the reaction mixture allowed to stand at room temperature 16 hours then concentrated. The resulting residue was twice dissolved in 15 mL absolute ethanol and concentrated leaving a foam that was purified by silica gel chromatography (4x4 cm silica gel, eluted w. 100 mL each of 10, 15 and 20% (MeOH/10% NH_4Cl)/ CH_2Cl_2 to give racemic ethyl 3-(6-aminopyridin-3-yl)-2-(1*H*-imidazol-4-yl)propanoate (**8-1**) as a foam. Further purification by preparative chiral HPLC (5x50 mm chiralpak AD, 70 mL/min, 50% MeOH in EtOH to 100% MeOH) afforded the resolved enantiomers.

Data for fast eluting compound: optical rotation:$[\alpha]_D^{24}$= -22.6° (c=0.40 in MeOH) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, 1H, *J*=1.83 Hz); 7.59 (s, 1H); 7.20 (br d, 1H, *J*=8.33 Hz); 6.88 (s, 1H); 6.40 (d, 1H, *J*=8.42 Hz); 4.33 (br s, 1H); 4.12 (m, 2H); 3.91 (t, 1H, *J*=7.78 Hz); 3.14 (dd, 1H, *J*=13.8 and 8.33 Hz); 3.05 (dd, 1H, *J*=13.6 and 7.14 Hz); 1.19 (t, 3H, *J*=7.14Hz).electrospray mass spectrum M+H=261.1. Data for slow eluting compound: optical rotation:$[\alpha]_D^{24}$= +24.8° (c=0.47 in MeOH) ^{1}H NMR and mass spec identical. to enantiomer.

(-) 3-(6-aminopyridin-3-yl)-2-(1*H*-imidazol-4-yl)propanoic acid dihydrochloride (**8-2**)

To a solution of 0.09g (0.35 mmol) (-) ethyl 3-(6-aminopyridin-3-yl)-2-(1*H*-imidazol-4-yl)propanoate (**8-1**)in 3 mL water was added 1 mL concentrated aqueous HCl and the resulting mixture heated to 80 °C for 1.5 hours, then concentrated. The residue was twice dissolved in 7 mL water and concentrated, then lyopholized from 1 mL water to give 3-(6-aminopyridin-3-yl)-2-(1*H*-imidazol-4-yl)propanoic acid (**8-2**)dihydrochloride. optical rotation:$[\alpha]_D^{23}$= -9.1° (c=0.44 in water) ^{1}H NMR (400 MHz, DMSO d_6) δ 9.06 (s, 1H); 8.01 (br s, 2H); 7.77 (m, 2H); 7.54 (s, 1H); 6.92 (d, 1H, *J*=9.71 Hz); 4.21 (dd, 1H, *J*=8.97 and 6.59 Hz); 3.21 (dd, 1H, *J*=14.3 and 6.59 Hz); 3.10 (dd, 1H, *J*=14.1 and 9.16 Hz); electrospray mass spectrum M+H=233.1.

ethyl 3-(6-aminopyridin-3-yl)-2-(1-butyl-1*H*-imidazol-4-yl)propanoate (**8-3**)

To a solution of 0.05g (0.19 mmol) ethyl 3-(6-aminopyridin-3-yl)-2-(1*H*-imidazol-4-yl)propanoate (**8-1**) in 0.5 mL DMF was added 7.7mg (0.19 mmol, 60% dispersion in mineral oil) sodium hydride. After 1 hour 0.022 mL (0.19mmol) butyl bromide was added, and after 30 minutes the reaction was quenched with 0.2 mL water. The resulting solution was purified directly by preparative reverse phase HPLC (20x150 mm C18 column, 5-95% AcN/H_2O (0.1%TFA) over 25 minutes). The product –containing fractions were concentrated and passed through a 1.5x10cm plug of silica gel, eluting with 5-15% MeOH(10% NH_4Cl)/ CH_2Cl_2 to give the free base that was further purified on a 1.5x10cm column of silica gel, eluting with 5-12% MeOH/toluene to afford ethyl 3-(6-aminopyridin-3-yl)-2-(1-butyl-1*H*-imidazol-4-yl)propanoate (**8-3**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, 1H, *J*=2.01 Hz); 7.37 (s, 1H); 7.23 (dd, 1H, *J*=8.43 and 2.38 Hz); 6.76 (s, 1H); 6.39 (d, 1H, *J*=8.33 Hz); 4.28 (br s, 2H); 4.10 (m, 2H); 3.85 (m, 3H); 3.14 (dd, 1H, *J*=13.9 and 8.7 Hz); 3.07 (dd,

1H, *J*=6.77 and 13.9 Hz); 1.73 (m, 2H); 1.30 (m, 2H); 1.16 (t, 3H, *J*=7.14 Hz); 0.93 (t, 3H, *J*=7.32 Hz). Electrospray mass spectrum M+H=317.1

3-(6-aminopyridin-3-yl)-2-(1-butyl-1*H*-imidazol-4-yl)propanoic acid dihydrochloride (**8-4**)

To a solution of 0.01g (0.03 mmol) ethyl 3-(6-aminopyridin-3-yl)-2-(1-butyl-1*H*-imidazol-4-yl)propanoate (**8-3**) in 0.25 mL water was added 0.25 mL concentrated aqueous HCl and the reaction mixture heated to 90 °C 6 hours, then concentrated and lyopholized from 1 mL water to give 3-(6-aminopyridin-3-yl)-2-(1-butyl-1*H*-imidazol-4-yl)propanoic acid dihydrochloride. ^{1}H NMR (400 MHz, DMSO d_6) δ 9.07 (s, 1H); 8.01 (br s, 2H); 7.76 (m, 2H); 7.61 (s, 1H), 6.89 (d, 1H, *J*=9.52 Hz); 4.18 (t, 1H, *J*=8.97 Hz); 4.11 (t, 2H, *J*=7.14); 3.66 (br s, 2H); 3.19 (dd, 1H, *J*=14.3 and 6.96 Hz); 3.06 (dd, 1H, *J*=13.91 and 9.15 Hz); 1.72 (q, 2H, *J*=6.96 Hz); 1.15 (m, 2H); 0.86 (t, 3H, *J*=7.33 Hz). Electrospray mass spectrum M+H=289.1

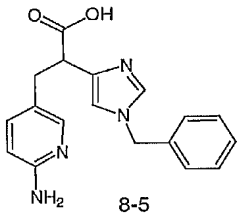
The following examples were prepared in the same manner as **8-4** except the appropriate alkyl bromide, alkyl iodide, alkyl triflate, or aryl fluoride was used in place of butyl bromide. :

#		IUPAC Name	Mass Spec
8-5		3-(6-aminopyridin-3-yl)-2-(1-benzyl-1*H*-imidazol-4-yl)propanoic acid	323
8-6		3-(6-aminopyridin-3-yl)-2-[1-(cyclohexylmethyl)-1*H*-imidazol-4-yl]propanoic acid	329
8-7		3-(6-aminopyridin-3-yl)-2-[1-(3-phenylpropyl)-1*H*-imidazol-4-yl]propanoic acid	351
8-8		3-(6-aminopyridin-3-yl)-2-[1-(cyclopropylmethyl)-1*H*-imidazol-4-yl]propanoic acid	287
8-9		3-(6-aminopyridin-3-yl)-2-[1-(2-piperidin-4-ylethyl)-1*H*-imidazol-4-yl]propanoic acid	344
8-10		3-(6-aminopyridin-3-yl)-2-[1-(2-phenylethyl)-1*H*-imidazol-4-yl]propanoic acid	337
8-11		3-(6-aminopyridin-3-yl)-2-[1-(2-ethylbutyl)-1*H*-imidazol-4-yl]propanoic acid	317

8-12		2-(1-allyl-1*H*-imidazol-4-yl)-3-(6-aminopyridin-3-yl)propanoic acid	273
8-13		3-(6-aminopyridin-3-yl)-2-(1-isobutyl-1*H*-imidazol-4-yl)propanoic acid	289
8-14		3-(6-aminopyridin-3-yl)-2-[1-(2-methoxyethyl)-1*H*-imidazol-4-yl]propanoic acid	291
8-15		3-(6-aminopyridin-3-yl)-2-[1-(cyclobutylmethyl)-1*H*-imidazol-4-yl]propanoic acid	301
8-16		3-(6-aminopyridin-3-yl)-2-(1-methyl-1*H*-imidazol-4-yl)propanoic acid	247
8-17		3-(6-aminopyridin-3-yl)-2-[1-(2,2-difluoro-2-pyridin-2-ylethyl)-1*H*-imidazol-4-yl]propanoic acid	374
8-18		3-(6-aminopyridin-3-yl)-2-[1-(3-methylbenzyl)-1*H*-imidazol-4-yl]propanoic acid	337
8-19		3-(6-aminopyridin-3-yl)-2-[1-(4-methylbenzyl)-1*H*-imidazol-4-yl]propanoic acid	337
8-20		3-(6-aminopyridin-3-yl)-2-[1-(4-cyanobenzyl)-1*H*-imidazol-4-yl]propanoic acid	348
8-21		3-(6-aminopyridin-3-yl)-2-[1-(3-methoxybenzyl)-1*H*-imidazol-4-yl]propanoic acid	353
8-22		3-(6-aminopyridin-3-yl)-2-(1-isopropyl-1*H*-imidazol-4-yl)propanoic acid	275
8-23		3-(6-aminopyridin-3-yl)-2-{1-[3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)propyl]-1*H*-imidazol-4-yl}propanoic acid	420
8-24		3-(6-aminopyridin-3-yl)-2-{1-[4-(trifluoromethyl) benzyl]-1*H*-imidazol-4-yl}propanoic acid	391
8-25		3-(6-aminopyridin-3-yl)-2-[1-(2-chlorobenzyl)-1*H*-imidazol-4-yl]propanoic acid	357
8-26		3-(6-aminopyridin-3-yl)-2-[1-(4-chlorobenzyl)-1*H*-imidazol-4-yl]propanoic acid	357
8-27		3-(6-aminopyridin-3-yl)-2-[1-(carboxymethyl)-1*H*-imidazol-4-yl]propanoic acid	291
8-28		3-(6-aminopyridin-3-yl)-2-[1-(2-methylbenzyl)-1*H*-imidazol-4-yl]propanoic acid	337

8-29		4-({4-[2-(6-aminopyridin-3-yl)-1-carboxyethyl]-1*H*-imidazol-1-yl}methyl)benzoic acid	367
8-30		3-(6-aminopyridin-3-yl)-2-[1-(3-chlorobenzyl)-1*H*-imidazol-4-yl]propanoic acid	357
8-31		3-(6-aminopyridin-3-yl)-2-{1-[3-(benzyloxy) propyl]-1*H*-imidazol-4-yl}propanoic acid	381
8-32		4-{4-[2-(6-aminopyridin-3-yl)-1-carboxyethyl]-1*H*-imidazol-1-yl}butanoic acid	319
8-33		3-(6-aminopyridin-3-yl)-2-[1-(pyridin-2-ylmethyl)-1*H*-imidazol-4-yl]propanoic acid	324
8-34		3-(6-aminopyridin-3-yl)-2-[1-(3,3-dimethylbutyl)-1*H*-imidazol-4-yl]propanoic acid	317
8-35		3-(6-aminopyridin-3-yl)-2-[1-(tetrahydrofuran-2-ylmethyl)-1*H*-imidazol-4-yl]propanoic acid	317
8-36		3-(6-aminopyridin-3-yl)-2-{1-[2-(1*H*-pyrrol-1-yl)ethyl]-1*H*-imidazol-4-yl}propanoic acid	326
8-37		3-(6-aminopyridin-3-yl)-2-(1-ethyl-1*H*-imidazol-4-yl)propanoic acid	261
8-38		3-(6-aminopyridin-3-yl)-2-(1-propyl-1*H*-imidazol-4-yl)propanoic acid	275
8-39		3-(6-aminopyridin-3-yl)-2-[1-(tetrahydro-2*H*-pyran-2-ylmethyl)-1*H*-imidazol-4-yl]propanoic acid	331
8-40		3-(6-aminopyridin-3-yl)-2-[1-(pyridin-3-ylmethyl)-1*H*-imidazol-4-yl]propanoic acid	324
8-41		3-(6-aminopyridin-3-yl)-2-[1-(4,4,4-trifluorobutyl)-1*H*-imidazol-4-yl]propanoic acid	343
8-42		3-(6-aminopyridin-3-yl)-2-(1-pentyl-1*H*-imidazol-4-yl)propanoic acid	303
8-43		3-(6-aminopyridin-3-yl)-2-[1-(4-nitrophenyl)-1*H*-imidazol-4-yl]propanoic acid	354
8-44		3-(6-aminopyridin-3-yl)-2-[1-(4-cyanophenyl)-1*H*-imidazol-4-yl]propanoic acid	334
8-45		3-(6-aminopyridin-3-yl)-2-[1-(2-cyanophenyl)-1*H*-imidazol-4-yl]propanoic acid	334

8-46		3-(6-aminopyridin-3-yl)-2-[1-(2-nitrophenyl)-1*H*-imidazol-4-yl]propanoic acid	354
8-47		3-(6-aminopyridin-3-yl)-2-(1-pyrimidin-2-yl-1*H*-imidazol-4-yl)propanoic acid	311
8-48		3-(6-aminopyridin-3-yl)-2-(1-hexyl-1*H*-imidazol-4-yl)propanoic acid	317



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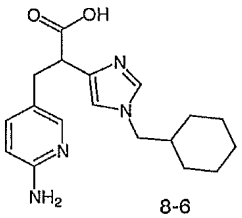

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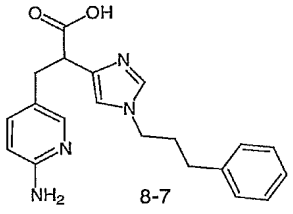

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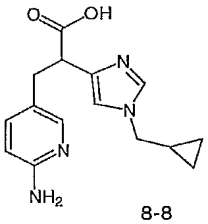

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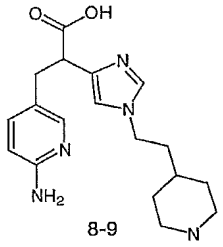

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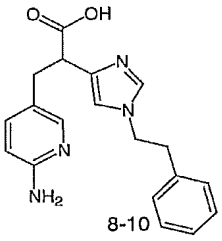

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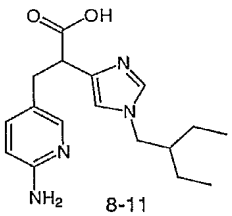

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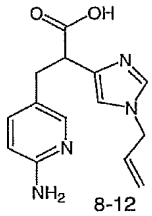

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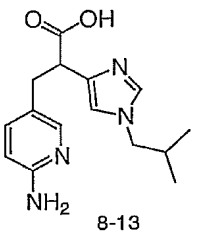
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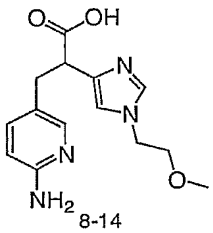
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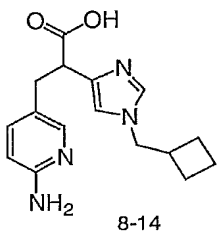
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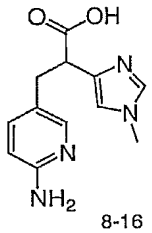
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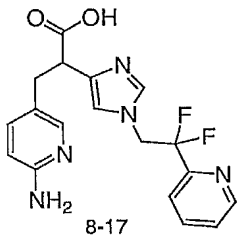
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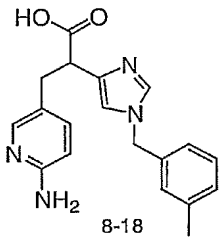
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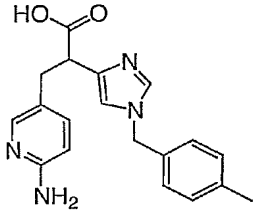
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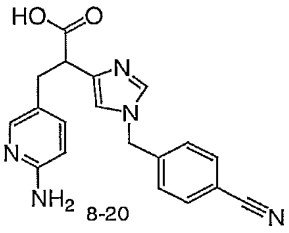
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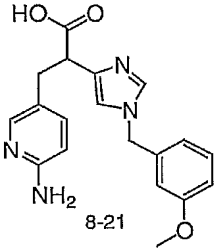
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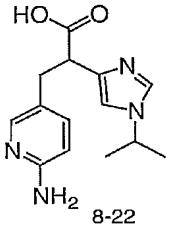
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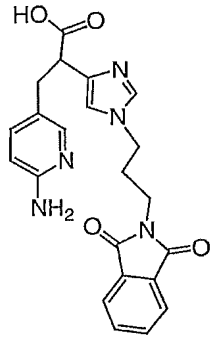
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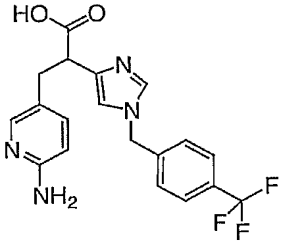
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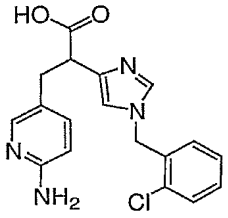
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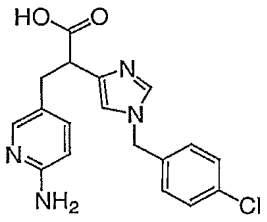
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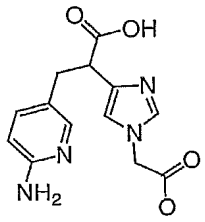
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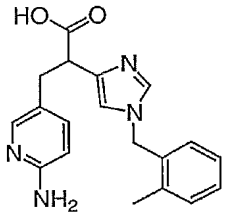
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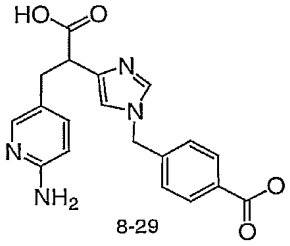
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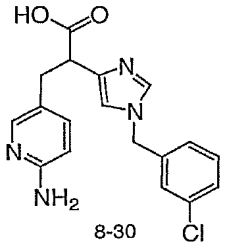
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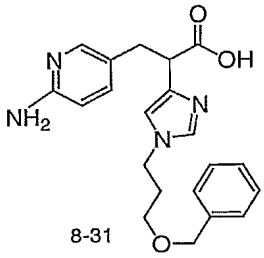
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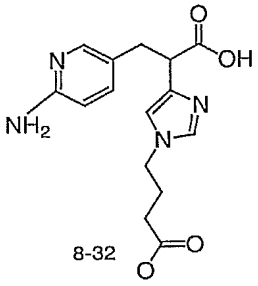
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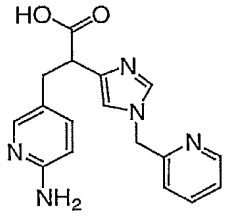
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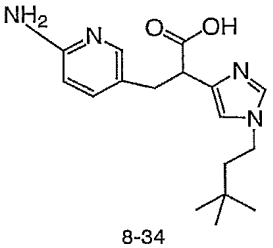
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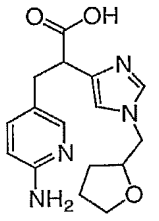
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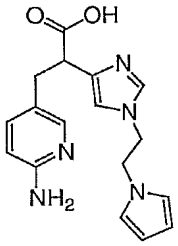
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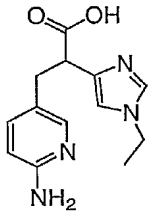
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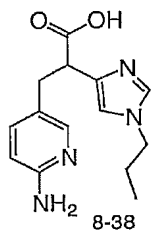
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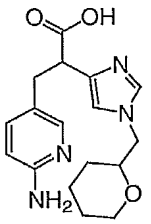
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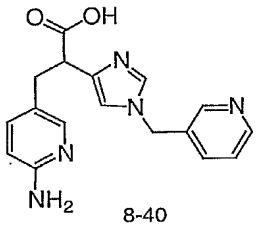
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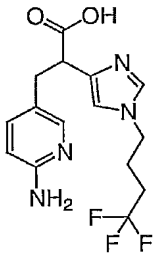
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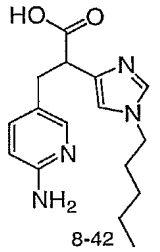
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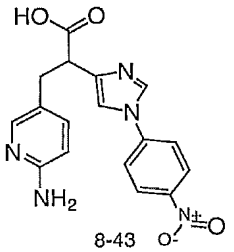
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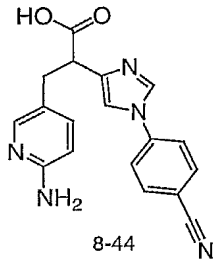
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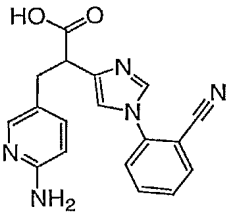
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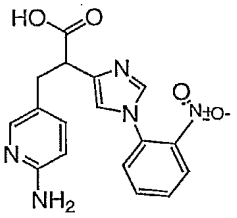
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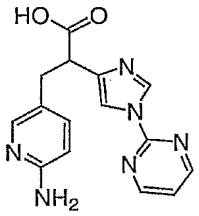
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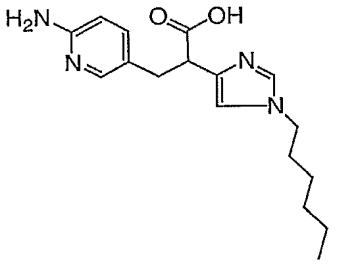
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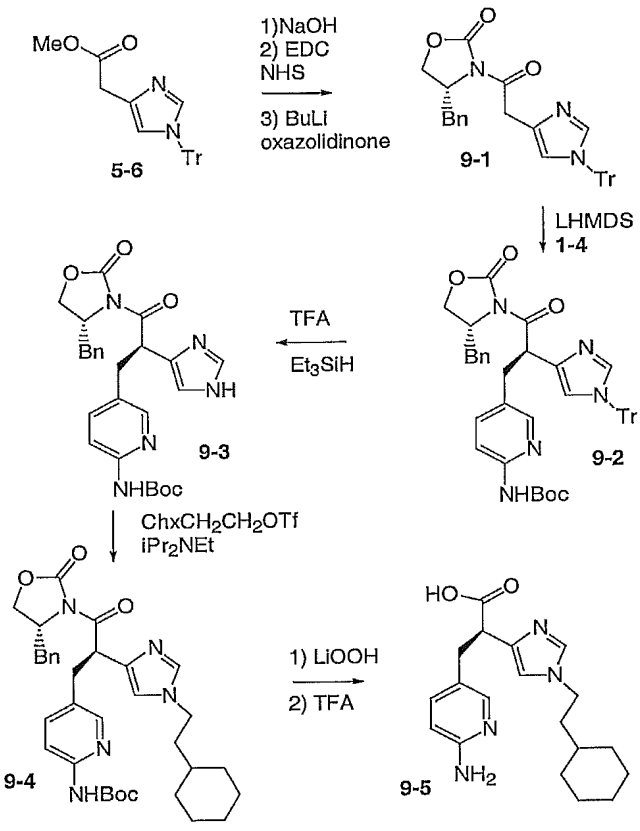
Scheme 9



(4*R*)-4-benzyl-3-[(1-trityl-1*H*-imidazol-4-yl)acetyl]-1,3-oxazolidin-2-one (**9-1**)

To a solution of 19.5g (51 mmol) methyl {1-[triphenylmethyl]-1*H*-imidazol-4-yl}acetate **5-6** in 150 mL THF was added 56 mL (56 mmol, 1M solution in water) NaOH and the reaction mixture stirred vigorously for 1 hour. The mixture was then poured into 1 L CH_2Cl_2 and 250 mL water and the pH of the aqueous layer was adjusted to pH 4. The layers were mixed and separated and the aqueous layer was extracted 4 x 200 mL CH_2Cl_2. The combined extracts were dried over Na_2SO_4, filtered, and concentrated to give 19g of {1-[triphenylmethyl]-1*H*-imidazol-4-yl}acetic acid as a tan solid of which 10.2g (27.6 mmol) was suspended in 300 mL CH_2Cl_2 and to this was added 3.8g (33 mmol) *N*-hydroxysuccinimide which caused the mixture to become homogeneous. To this was added 8g (42 mmol) EDC and the reaction mixture was allowed to stir for 3 hours, then was diluted with 700 mL

CH_2Cl_2, washed with 600 mL water, 600 mL brine, dried over Na_2SO_4, filtered, and concentrated. The residue was dissolved in 200 mL THF and cooled to –78 °C. To this was added a –78 °C mixture of 4.9g (28 mmol) (*R*) 4-benzyl-2-oxazolidinone and 11 mL (28 mmol, 2.5M solution in hexane) butyllithium in 100 mL THF via large-bore cannula over 1 minute. The reaction mixture was allowed to stir for 30 minutes at –78 °C, then allowed to warm with the dry ice bath to 0 °C over 2 hours then quenched by pouring into 700 mL EtOAc. This was washed 2x600 mL water, 1x600 mL brine, dried over Na_2SO_4, filtered, and concentrated. Purification by automated flash chromatography (300g silica gel cartridge, 100 mL/min of a linear gradient 0-5% MeOH/ CH_2Cl_2 over 30 min) followed by repurification of mixed fractions (120g silica gel cartridge, 90 mL/min of a linear gradient 2-5% MeOH/ CH_2Cl_2 over 30 min) provided 11g (75%) (4*R*)-4-benzyl-3-[(1-trityl-1*H*-imidazol-4-yl)acetyl]-1,3-oxazolidin-2-one **9-1**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, 1H, *J*=1.46 Hz); 7.35-7.29 (m, 12H); 7.20 (m, 2H); 7.16 (m, 6H); 6.78 (d, 1H, *J*=1.28 Hz); 4.63 (m, 1H); 4.28 (d, 1H, *J*=17.4 Hz); 4.21 (d, 1H, *J*=18.4 Hz); 4.16 (m, 2H); 3.34 (dd, 1H, *J*=13.4 and 3.28 Hz); 2.72 (dd, 1H, *J*=13.4 and 9.89 Hz). Electrospray Mass Spectrum (M+H=528.2)

tert-butyl 5-[(2*R*)-3-[(4*R*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]-3-oxo-2-(1-trityl-1*H*-imidazol-4-yl)propyl]pyridin-2-ylcarbamate (**9-2**)

To a solution of 5.5g (10.4 mmol) (4*R*)-4-benzyl-3-[(1-trityl-1*H*-imidazol-4-yl)acetyl]-1,3-oxazolidin-2-one **9-1** in 100 mL THF at –100 °C was added 11.5 mL (11.5 mmol, 1 M solution in THF) LHMDS slowly so the reaction mixture was maintained between –98 °C and –100 °C. Five minutes after the addition was complete, a –78 °C solution of 3g (10.4 mmol) *tert*-butyl 5-(bromomethyl)pyridin-2-ylcarbamate (**1-4**) in 75 mL THF was added slowly so the reaction mixture was maintained between –95 °C and –100 °C. The reaction mixture was then allowed to warm to –78 °C with the bath (20 min) and then maintained at –78 °C for 3 hours before pouring into a well stirred mixture of 700 mL EtOAc/ 500 mL water. The layers were mixed and separated and the organic layer was washed with 500 mL water, 500 mL brine, dried over Na_2SO_4, filtered, and concentrated. Purification by automated flash chromatography (300g silica gel cartridge, 100 mL/min of a linear gradient 0.5-5% MeOH/ CH_2Cl_2 over 30 min) provided 7g *tert*-butyl 5-[(2*R*)-3-[(4*R*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]-3-oxo-2-(1-trityl-1*H*-imidazol-4-yl)propyl]pyridin-2-ylcarbamate **9-2** as a 4:1 mixture of diastereomers that were

separated in the next step. ^{1}H NMR (major isomer) (400 MHz, $CDCl_3$) δ 8.06 (d, 1H, *J*=2.02 Hz); 7.82 (d, 1H, *J*=8.42 Hz); 7.72 (br s, 1H); 7.46 (dd, 1H, *J*=8.43 and 2.2 Hz); 7.37 (d, 1H, *J*=1.28 Hz); 7.29 (m, 12H); 7.12 (m, 2H); 7.05 (m, 6H); 6.58 (d, 1H, *J*=1.28 Hz); 5.14 (dd, 1H, *J*=6.96 and 8.42 Hz); 4.65 (m, 1H); 4.08(m, 2H); 3.33 (dd, 1H, *J*=13.7 and 6.78 Hz); 3.29 (m, 2H); 2.67 (dd, 1H, *J*=13.2 and 9.71 Hz); 1.5 (s, 9H). Electrospray Mass Spectrum (M+H=734.3)

tert-butyl 5-[(2*R*)-3-[(4*R*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]-3-oxo-2-(1*H*-imidazol-4-yl)propyl]pyridin-2-ylcarbamate (**9-3**)

To a 0 °C solution of 7g (9.5 mmol) *tert*-butyl 5-[(2*R*)-3-[(4*R*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]-3-oxo-2-(1-trityl-1*H*-imidazol-4-yl)propyl]pyridin-2-ylcarbamate (**9-2**) in 120 mL CH_2Cl_2 was added 1.68 mL (10.5 mmol) triethylsilane and 7.4 mL (95 mmol) TFA and the reaction mixture was kept at 0 °C for 4 hours then warmed to room temperature for 1.5 hours, then quenched by pouring into a mixture of 500 mL CH_2Cl_2, 300 mL water, and 100 mL 1N NaOH. The layers were mixed and separated and the organic layer was washed 300 mL brine, dried over Na_2SO_4, filtered, and concentrated. Purification by automated flash chromatography (120g silica gel cartridge, 90 mL/min of a linear gradient 1-10% MeOH/ CH_2Cl_2 over 30 min) followed by repurification of mixed fractions (90g silica gel cartridge, 70 mL/min of a linear gradient 2-10% MeOH/ CH_2Cl_2 over 30 min) provided 2.6g *tert*-butyl 5-[(2*R*)-3-[(4*R*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]-3-oxo-2-(1*H*-imidazol-4-yl)propyl]pyridin-2-ylcarbamate (**9-3**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, 1H, *J*=1.46 Hz); 7.79 (m, 2H); 7.59 (br s, 1H); 7.50 (dd, 1H, *J*=8.6 and 2.0 Hz); 7.26 (m, 3H); 7.05 (br d, 2H, *J*=6.4 Hz); 6.87 (br s, 1H); 5.33 (t, 1H, *J*=7.7 Hz); 4.64 (m, 1H); 4.09 (d, 2H, *J*=5.1 Hz); 3.39 (dd, 1H, *J*=13.7 and 7.7 Hz); 3.16 (m, 2H); 2.66 (dd, 1H, *J*=13.4 and 9.3 Hz) 1.5 (s, 9H). Electrospray Mass Spectrum M+H=492.3

tert-butyl 5-{(2*R*)-3-[(4*R*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]-2-[1-(2-cyclohexylethyl)-1*H*-imidazol-4-yl]-3-oxopropyl}pyridin-2-ylcarbamate (**9-4**)

To a 0 °C solution of 1.1 mL (7.8 mmol) 2-cyclohexylethanol was added 1 mL (9 mmol) 2,6-lutidine followed by dropwise addition of 1.44 mL (8.6 mmol) trifluoromethanesulfonic anhydride. The reaction mixture was allowed to stir 1 hour at 0 °C, hexane was added and the mixture was filtered through celite (hexane rinse). The filtrate was concentrated to give 1.5g 2-cyclohexylethyl

trifluoromethanesulfonate that was used immediately. . ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.58 (t, 2H, *J*=6.78 Hz); 1.72 (m, 7H); 1.45 (m, 1H); 1.32-1.1 (m, 3H); 0.95 (m, 2H).

To a solution of 0.1 g (0.2 mmol) *tert*-butyl 5-[(2*R*)-3-[(4*R*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]-3-oxo-2-(1*H*-imidazol-4-yl)propyl]pyridin-2-ylcarbamate (**9-3**) in 1 mL CH_2Cl_2 was added 40 µL (0.2 mmol) iPr_2NEt and 0.05g (0.2 mmol) 2-cyclohexylethyl trifluoromethanesulfonate. The reaction mixture was allowed to stir 16 hours, then another 0.02g (0.08 mmol) 2-cyclohexylethyl trifluoromethanesulfonate was added. The reaction mixture was then stirred 2 more hours, diluted with 75 mL CH_2Cl_2, washed with 50 mL saturated aqueous sodium bicarbonate solution, 50 mL brine, dried over Na_2SO_4, filtered, and concentrated. Purification by automated flash chromatography (40g silica gel cartridge, 40 mL/min of a linear gradient 1-7% MeOH/ CH_2Cl_2 over 15 min) provided 0.056g *tert*-butyl 5-{(2*R*)-3-[(4*R*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]-2-[1-(2-cyclohexylethyl)-1*H*-imidazol-4-yl]-3-oxopropyl}pyridin-2-ylcarbamate (**9-4**). . ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, 1H, *J*=2.2 Hz); 7.80 (d, 1H, *J*=8.42 Hz); 7.52 (dd, 1H, *J*=8.6 and 2.38 Hz); 7.38 (d, 1H, *J*=1.1 Hz); 7.26 (m, 3H); 6.9 (m, 2H); 6.73 (d, 1H, *J*=1.28 Hz); 5.27 (t, 1H, *J*=7.69 Hz); 4.66 (m, 1H); 4.11 (m, 2H); 3.84 (t, 2H, *J*=7.33 Hz); 3.41 (dd, 1H, *J*=13.7 and 7.88 Hz); 3.21 (m, 2H); 2.65 (dd, 1H, *J*=13.4 and 9.52 Hz); 1.7-1.6 (m, 8H); 1.5 (s, 9H); 1.17 (m, 3H); 0.93 (m, 2H). Electrospray Mass Spectrum (M+H=602.3).

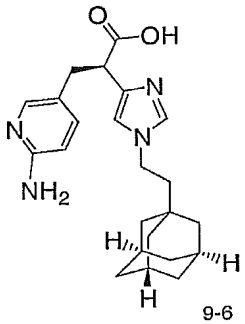
(2*R*)-3-(6-aminopyridin-3-yl)-2-[1-(2-cyclohexylethyl)-1*H*-imidazol-4-yl]propanoic acid (**9-5**)

To a solution of 0.056g (0.09 mmol) *tert*-butyl 5-{(2*R*)-3-[(4*R*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]-2-[1-(2-cyclohexylethyl)-1*H*-imidazol-4-yl]-3-oxopropyl}pyridin-2-ylcarbamate (**9-4**) in 1 mL THF was added a mixture of 0.1 mL LiOH (0.1 mmol, 1M aqueous solution) and 0.01 mL (0.1 mmol, 30% w/w solution in water) H_2O_2 and the resulting mixture was allowed to stir for 4 hours, then 0.14 mL (0.14 mmol, 1M aqueous solution) Na_2SO_3 was added and the reaction mixture was allowed to stir 30 more minutes. This was then diluted with 0.3 mL water and 0.3 mL DMSO, filtered through a 0.45 µM syringe filter and purified by automated reverse phase HPLC (20x150 mm C18 column, 0-95% CH_3CN/H_2O (0.1%TFA) over 25 minutes) provided 0.035g (2*R*)-3-{6-[(*tert*-butoxycarbonyl)amino]pyridin-3-yl}-2-[1-(2-cyclohexylethyl)-1*H*-imidazol-4-yl]propanoic acid which was treated with 1 mL

TFA for 1 hour. The residue was concentrated and purified by ion exchange chromotography (1g Varian SCX cartridge, load in 1:1 acetonitrile:water, rinse with 10 mL acetonitrile, elute with 3 mL NH_3/MeOH.) to afford 13 mg (2*R*)-3-(6-aminopyridin-3-yl)-2-[1-(2-cyclohexylethyl)-1*H*-imidazol-4-yl]propanoic acid (**9-5**). ^{1}H NMR (400 MHz, $DMSOd_6$) δ 7.67 (br s , 1H); 7.51 (s, 1H); 7.13 (br d, 1H, *J*=8.42 Hz); 6.96 (s, 1H); 6.30 (d, 1H, *J*=8.25 Hz); 5.63 (d, 1H, *J*=6.41 Hz); 3.91 (t, 2H, *J*=8.06 Hz); (t, 1H, *J*=7.88 Hz); 2.92 (dd, 1H, *J*=13.5 and 8.42 Hz); 2.83 (dd, 1H, *J*=13.7 and 6.59 Hz); 1.7-1.54 (m, 8H); 1.15 (m, 3H); 0.91 (m, 2H). High resolution mass spectrum FT/ICR (7T) M+H calculated 343.2128 found 343.2120.

The following compounds were prepared similarly:

#		Name	Mass Spec
9-6		(2*R*)-2-{1-[2-(1-adamantyl)ethyl]-1*H*-imidazol-4-yl}-3-(6-aminopyridin-3-yl)propanoic acid	395
9-7		(2*R*)-3-(6-aminopyridin-3-yl)-2-[1-(2-cyclopropylethyl)-1*H*-imidazol-4-yl]propanoic acid	301
9-8		(2*R*)-3-(6-aminopyridin-3-yl)-2-{1-[2-(6,6-dimethylbicyclo[3.1.1]hept-2-yl)ethyl]-1*H*-imidazol-4-yl}propanoic acid	383
9-9		(2*R*)-3-(6-aminopyridin-3-yl)-2-(1-{2-[(1*S*,4*R*)-bicyclo[2.2.1]hept-2-yl]ethyl}-1*H*-imidazol-4-yl)propanoic acid	355



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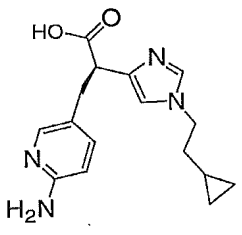
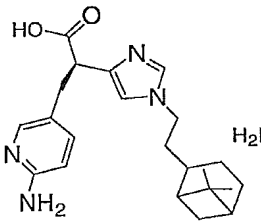


9-7



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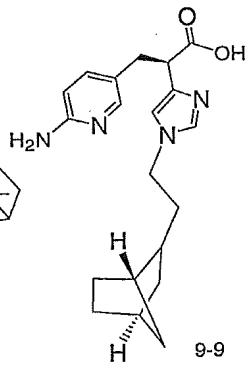
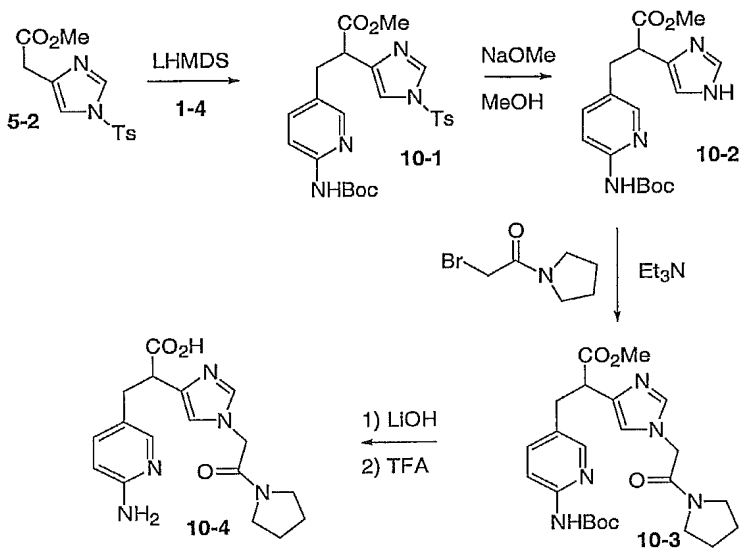


9-9

Scheme 10



methyl 3-{6-[(tert-butoxycarbonyl)amino]pyridin-3-yl}-2-{1-[(4-methylphenyl)sulfonyl]-1H-imidazol-4-yl}propanoate (**10-1**)

To a solution of methyl 2-{1-[(4-methylphenyl)sulfonyl]-1H-imidazol-4-yl}acetate (**5-2**) (4.2 g, 14.3 mmol) in THF (400 mL) cooled to –78 °C was added lithium hexamethyldisylazide (15.7 mL, 15.7 mmol, 1M in THF) in 5 ml portions over 3 min. The orange solution was stirred at –78 °C for 5 min and *tert*-butyl-5-(bromomethyl)-pyridin-2-ylcarbamate (2.75 g, 9.5 mmol) added in one portion. The reaction mixture was stirred at –78 °C for 1h and allowed to warm to room temperature. The reaction mixture was poured in a mixture of ethyl acetate and aqueous sodium bicarbonate. The organic layer was separated, washed with brine, dried over magnesium sulfate and concentrated in vacuo. The residual solid was triturated with ethyl acetate, filtered, washed with ethyl acetate and air dried to yield methyl 3-{6-[(tert-butoxycarbonyl)amino]pyridin-3-yl}-2-{1-[(4-methylphenyl)sulfonyl]-1H-imidazol-4-yl}propanoate (**10-1**) (4 g) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.98-7.92 (m, 2H); 7.77 (d, 2H, , J = 8.5Hz); 7.72 (d, 1H, , J = 8.7 Hz); 7.44 (br s, 1 H); 7.37 (d, 2H, J = 8.5 Hz); 7.28-7.22 (m, 1H); 7.11 (s, 1H); 3.84 (X of ABX,apparent t, 1H, J = 7.9 Hz); 3.63 (s, 3H); 3.19 (A of ABX, dd, 1H, J = 14.5, 7.9 Hz); 3.09 (B of ABX, dd, 1H, J = 14.5, 7.9 Hz); 2.45 (s, 3H); 1.52 (s, 9H). electrospray mass spectrum M+H=501.1.

methyl 3-{6-[(tert-butoxycarbonyl)amino]pyridin-3-yl}-2-(1H-imidazol-4-yl)propanoate (**10-2**):

To a suspension of methyl 3-{6-[(tert-butoxycarbonyl)amino]pyridin-3-yl}-2-{1-[(4-methylphenyl)sulfonyl]-1H-imidazol-4-yl}propanoate (**10-1**) (7.24 g, 14.5 mmol) in 1:1 THF:MeOH (200 mL) was added 30% NaOMe (131 uL, 0.72 mmol) and reaction mixture was stirred at room temperature for 75 minutes after which it exists as a clear solution.. The reaction mixture was concentrated in vacuo, and purified by flash chromatography (silica gel, 300 g, 4% to 10% MeOH containing 10% NH_4OH in dichloromethane) to give methyl 3-{6-[(tert-butoxycarbonyl)amino]pyridin-3-yl}-2-(1H-imidazol-4-yl)propanoate (**10-2**) (4.43 g) as a white solid. ^1H NMR ($CDCl_3$, 400 MHz): δ 9.55 (br s, 1H); 7.99 (d, 1H, , J = 2.1 Hz); 7.80 (d, 1H, , J = 8.6 Hz); 7.68 (s, 1H); 7.59 (s, 1H); 7.40 (dd, 1H, , J = 8.7, 2.1 Hz); 6.84 (s, 1H); 3.94 (X of ABX,apparent t, 1H, J = 7.9 Hz); 3.66 (s, 3H); 3.25 (A of ABX, dd, 1H, J = 13.6, 7.9 Hz); 3.21-3.10(B of ABX, br dd, 1H); 1.52 (s, 9H).

methyl 3-{6-[(tert-butoxycarbonyl)amino]pyridin-3-yl}-2-[1-(2-oxo-2-pyrrolidin-1-ylethyl)-1H-imidazol-4-yl]propanoate (**10-3**)

To a solution of methyl 3-{6-[(tert-butoxycarbonyl)amino]pyridin-3-yl}-2-(1H-imidazol-4-yl)propanoate (**10-2**) (300 mg, 0.87 mmol) in DMF (3 mL) was added diisopropylethyl amine (302 uL, 1.73 mmol) and 2-oxo-2-pyrrolidin-ethyl bromide (300 mg, 1.56 mmol, prepared from pyrrolidine and bromoacetyl bromide) in DMF (0.2 mL). The reaction mixture was stirred at room temperature for 20 h.. Aqueous LiCl was added and the reaction mixture extracted 5 times with ethyl acetate. The combined organic layers were dried over sodium sulfate, concentrated in vacuo, and purified by flash chromatography (silica gel, 90 g, 4% to 8% MeOH containing 10% NH_4OH in dichloromethane) to give methyl 3-{6-[(tert-butoxycarbonyl)amino]pyridin-3-yl}-2-[1-(2-oxo-2-pyrrolidin-1-ylethyl)-1H-imidazol-4-yl]propanoate (**10-3**) (121 mg) as a white solid.^1H NMR ($CDCl_3$, 400 MHz): δ 8.02 (d, 1H, , J = 2.5 Hz); 7.79 (d, 1H, , J = 8.8 Hz); 7.47 (s, 1H); 7.43 (dd, 1H, , J = 8.8, 2.5 Hz); 6.83 (s, 1H); 4.61 (s, 2H); 3.90 (X of ABX,dd, 1H, J = 8.8, 6.9 Hz); 3.63 (s, 3H); 3.52 (t, 2H, J = 7.2 Hz); 3.39 (t, 2H, J = 7.2 Hz); 3.25 (A of ABX, dd, 1H, J = 14.5, 8.5 Hz); 3.17 (B of ABX, dd, 1H, J = 14.5, 6.9 Hz); 2.07-1.77 (m, 2H); 1.93-1.84 (m, 2H); 1.52 (s, 9H). Electrospray Mass Spectrum M+H=458.7.

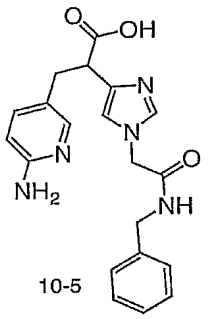
3-(6-aminopyridin-3-yl)-2-[1-(2-oxo-2-pyrrolidin-1-ylethyl)-1H-imidazol-4-yl]propanoic acid (**10-4**)

To a solution of methyl 3-{6-[(tert-butoxycarbonyl)amino]pyridin-3-yl}-2-[1-(2-oxo-2-pyrrolidin-1-ylethyl)-1H-imidazol-4-yl]propanoate (**10-3**) (110 mg, 0.24 mmol) in THF (1 mL) was added 1N LiOH (264 uL, 0.264 mmol) and the reaction mixture stirred at room temperature for 30 min. after which time 1N HCl (264 uL, 0.264 mmol) was added. The THF was removed under a stream of nitogen and the residual aqueous solution purified by reverse phase preparative HPLC (20x150 mm YMC C18 PRO, 5% to 95% aqueous CH_3CN containing 0.1% TFA) to provide methyl 3-{6-[(tert-butoxycarbonyl)amino]pyridin-3-yl}-2-[1-(2-oxo-2-pyrrolidin-1-ylethyl)-1H-imidazol-4-yl]propanoic acid which was treated with 1 mL TFA at room temperature for 1h15 to give 3-(6-aminopyridin-3-yl)-2-[1-(2-oxo-2-pyrrolidin-1-ylethyl)-1H-imidazol-4-yl]propanoic acid bis TFA salt (**10-4**) (95 mg) as a white solid after concentration in vacuo and subsequent liophilization. ^{1}H NMR (D_2O, 400 MHz): δ 8.61 (br s, 1H); 7.60 (dd, 1H, , J = 9.9, 2.6 Hz); 7.46 (br s, 1H); 7.25 (br s, 1H); 6.82 (d, 1H, , J = 9.9 Hz); 5.04 (s, 2H); 4.13 (X of ABX, app t, 1H, J = 7.9 Hz); 3.29 (t, 2H, J = 7.2 Hz); 3.31 (t, 2H, J = 7.2 Hz); 3.20 (A of ABX, dd, 1H, J = 14.8, 7.9 Hz); 3.20 (B of ABX, dd, 1H, J = 14.8, 7.9 Hz); 1.93-1.83 (m, 2H); 1.81-1.71 (m, 2H). Electrospray Mass Spectrum M+H=344.6.

The following compounds were prepared in a similar manner:

#		name	Mass spec
10-5		3-(6-aminopyridin-3-yl)-2-{1-[2-(benzylamino)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid	380.6
10-6		3-(6-aminopyridin-3-yl)-2-(1-{2-oxo-2-[(2-phenylethyl)amino]ethyl}-1*H*-imidazol-4-yl)propanoic acid	394.6
10-7		3-(6-aminopyridin-3-yl)-2-(1-{2-[(4-methoxyphenyl)amino]-2-oxoethyl}-1*H*-imidazol-4-yl)propanoic acid	396.6
10-8		3-(6-aminopyridin-3-yl)-2-{1-[2-(methylamino)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid	304.6
10-9		3-(6-aminopyridin-3-yl)-2-{1-[2-oxo-2-(4-phenylpiperidin-1-yl)ethyl]-1*H*-imidazol-4-yl}propanoic acid	434.6
10-10		3-(6-aminopyridin-3-yl)-2-{1-[2-(ethylamino)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid	318.6

10-11		3-(6-aminopyridin-3-yl)-2-{1-[2-(diethylamino)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid	346.7
10-12		3-(6-aminopyridin-3-yl)-2-[1-(2-anilino-2-oxoethyl)-1*H*-imidazol-4-yl]propanoic acid	366.6
10-13		3-(6-aminopyridin-3-yl)-2-[1-(2-oxo-2-piperidin-1-ylethyl)-1*H*-imidazol-4-yl]propanoic acid	358.6
10-14		3-(6-aminopyridin-3-yl)-2-(1-{2-oxo-2-[(3-phenylpropyl)amino]ethyl}-1*H*-imidazol-4-yl)propanoic acid	408.7
10-15		3-(6-aminopyridin-3-yl)-2-{1-[2-(1,1'-biphenyl-4-ylamino)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid	442.6
10-16		3-(6-aminopyridin-3-yl)-2-{1-[2-(2-naphthylamino)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid	416.0
10-17		3-(6-aminopyridin-3-yl)-2-{1-[2-(cyclohexylamino)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid	372.0
10-18		3-(6-aminopyridin-3-yl)-2-{1-[2-(dimethylamino)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid	318.6
10-19		3-(6-aminopyridin-3-yl)-2-[1-(1-methyl-2-oxo-2-pyrrolidin-1-ylethyl)-1*H*-imidazol-4-yl]propanoic acid	358.6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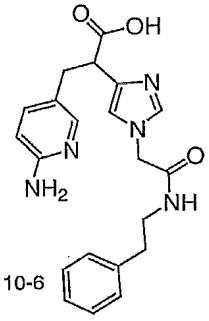
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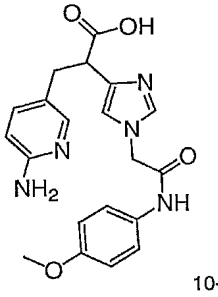
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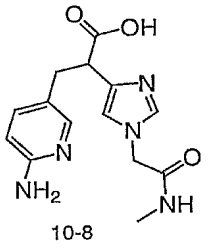
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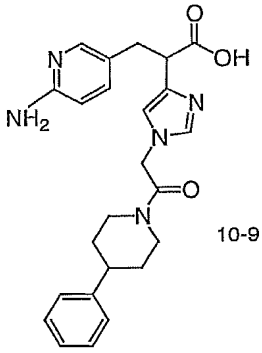
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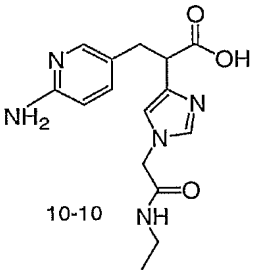
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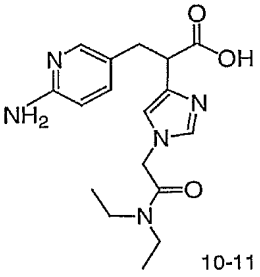
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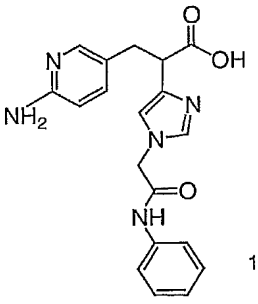
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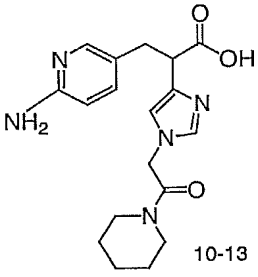
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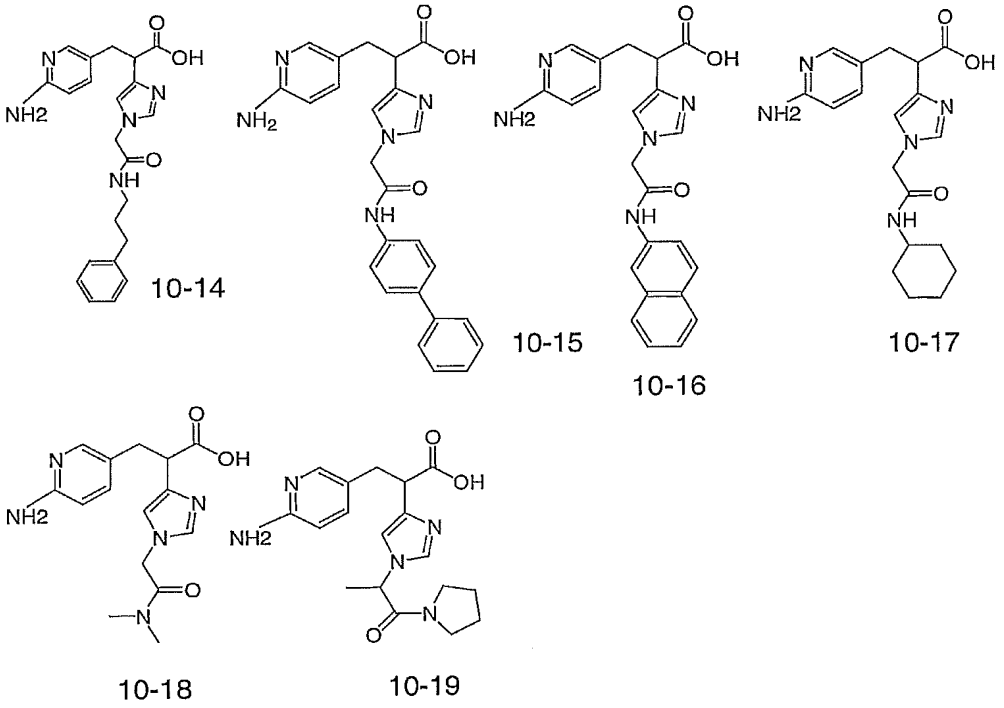
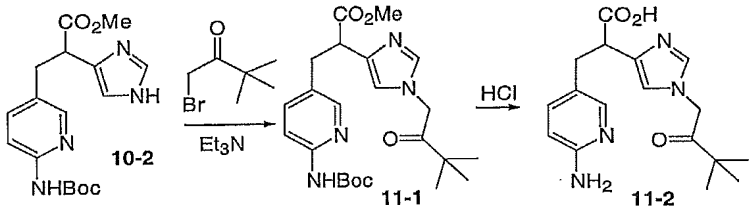


Scheme 11



Methyl 3-{6-[(tert-butoxycarbonyl)amino]pyridin-3-yl}-2-[1-(3,3-dimethyl-2-oxobutyl)-1H-imidazol-4-yl]propanoate (**11-1**):

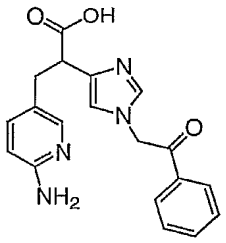
To a stirred solution of methyl 3-{6-[(tert-butoxycarbonyl)amino]pyridin-3-yl}-2-(1H-imidazol-4-yl)propanoate (**10-2**) (125 mg, 0.36 mmol) in DMF (0.5 ml) was added diisopropylethyl amine (50 uL, 0.36 mmol) and 1-bromopinacolone (49 uL, 0.36 mmol). The reaction mixture was stirred at room temperature for 20 h at which time aqueous LiCl was added and the reaction

mixture extracted 5 times with ethyl acetate. The combined organic layers were dried over sodium sulfate, concentrated in vacuo and purified by flash chromatography (silica gel, 20 g, 0% to 5% MeOH in dichloromethane) to give methyl 3-{6-[(tert-butoxycarbonyl)amino]pyridin-3-yl}-2-[1-(3,3-dimethyl-2-oxobutyl)-1H-imidazol-4-yl]propanoate (**11-1**) (85 mg) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99 (s, 1H); 7.77 (d, 1H, J = 8.7 Hz); 7.40 (dd, 1H, J = 7.4, 2.2 Hz); 6.68 (s, 1H); 4.82 (s, 2H); 3.89 (X of ABX, app t, 2H, J = 7.7 Hz); 3.63 (s, 3H); 3.20 (A of ABX, 1H, J = 14.8, 7.5 Hz); 3.19 (B of ABX, 1H, J = 14.8, 7.7 Hz); 1.51 (s, 9H); 1.24 (s, 9H).Electrospray Mass Spectrum M+H=445.6.

3-(6-Aminopyridin-3-yl)-2-[1-(3,3-dimethyl-2-oxobutyl)-1H-imidazol-4-yl]propanoic acid: (**11-2**)

To a flask containing methyl 3-{6-[(tert-butoxycarbonyl)amino]pyridin-3-yl}-2-[1-(3,3-dimethyl-2-oxobutyl)-1H-imidazol-4-yl]propanoate (**11-1**) (83 mg, 0.24 mmol), was added 0.5 mL of 6N hydrochloric acid. The flask was fitted with a condenser and placed in a 95 °C oil bath for 1.5 to 2.0 hrs. The mixture was concentrated to dryness in vacuo and the resulting solid treated with acetonitrile and subsequently the solvent evaporated to remove residual hydrochloric acid (2 x 5 mL) to provide the bis hydrochloride salt of 3-(6-aminopyridin-3-yl)-2-[1-(3,3-dimethyl-2-oxobutyl)-1H-imidazol-4-yl]propanoic acid (**11-2**) as a white solid. ^{1}H NMR (D_2O, 400 MHz): δ 8.49 (d, 1H, J = 1.4 Hz); 7.60 (dd, 1H, J = 9.2, 1.9 Hz); 7.43 (s, 1H); 7.07 (s, 1H); 6.82 (d, 1H, J = 9.2 Hz); 5.35 (s, 2H); 3.94 (X of ABX, app t, 1H, J = 7.8 Hz); 3.14 (A of ABX, dd, 1H, J = 14.3, 7.2 Hz); 2.95 (B of ABX, dd, 1H, J = 14.2, 8.3 Hz); 1.11 (s, 9H). Electrospray Mass Spectrum M+H=331.7.

#		name	Mass spec
11-3		3-(6-aminopyridin-3-yl)-2-[1-(2-oxo-2-phenylethyl)-1*H*-imidazol-4-yl]propanoic acid	351
11-4		3-(6-aminopyridin-3-yl)-2-{1-[2-(4-chlorophenyl)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid	385
11-5		3-(6-aminopyridin-3-yl)-2-{1-[2-(4-fluorophenyl)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid	369
11-6		3-(6-aminopyridin-3-yl)-2-{1-[2-(1,1'-biphenyl-4-yl)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid	427
11-7		3-(6-aminopyridin-3-yl)-2-{1-[2-(4-cyanophenyl)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid	376
11-8		3-(6-aminopyridin-3-yl)-2-{1-[2-(4-methoxyphenyl)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid	381
11-9		3-(6-aminopyridin-3-yl)-2-{1-[2-(2-methoxyphenyl)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid	381
11-10		2-{1-[2-(1-adamantyl)-2-oxoethyl]-1*H*-imidazol-4-yl}-3-(6-aminopyridin-3-yl)propanoic acid	409
11-11		3-(6-aminopyridin-3-yl)-2-{1-[2-(4-methylphenyl)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid	365
11-12		2-{1-[2-(4-aminophenyl)-2-oxoethyl]-1*H*-imidazol-4-yl}-3-(6-aminopyridin-3-yl)propanoic acid	366.6
11-13		3-(6-aminopyridin-3-yl)-2-[1-(1-methyl-2-oxo-2-phenylethyl)-1*H*-imidazol-4-yl]propanoic acid	365
11-14		3-(6-aminopyridin-3-yl)-2-{1-[2-(2-naphthyl)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid	401.6
11-15		3-(6-aminopyridin-3-yl)-2-{1-[2-(2,4-dimethyl phenyl)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid	379.6
11-16		3-(6-aminopyridin-3-yl)-2-(1-{2-oxo-2-[4-(trifluoromethyl) phenyl]ethyl}-1*H*-imidazol-4-yl)propanoic acid	419



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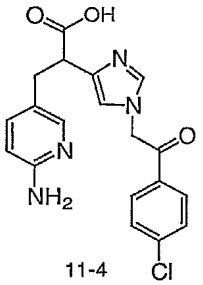

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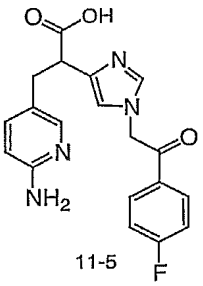

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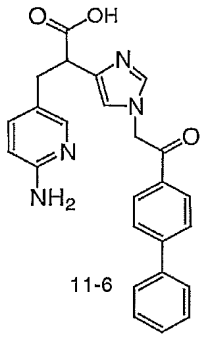

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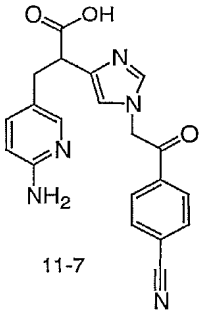

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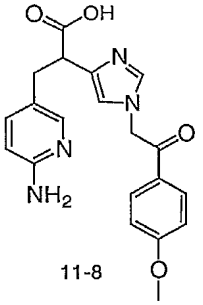

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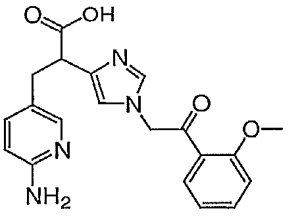

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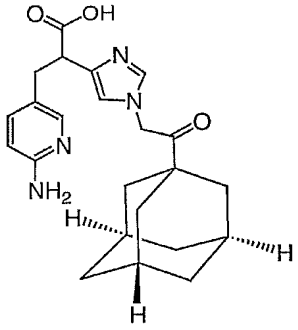
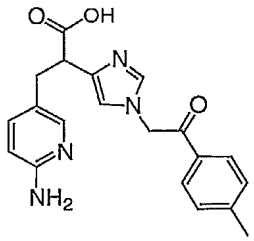
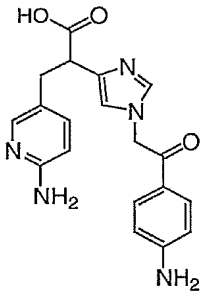


11-10



11-11



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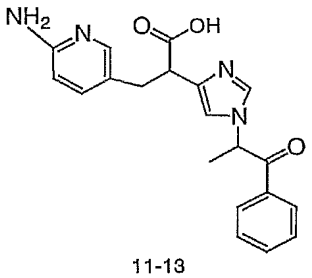
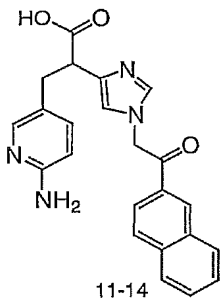
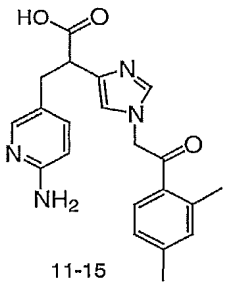


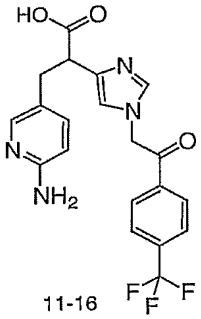
11-13



11-14

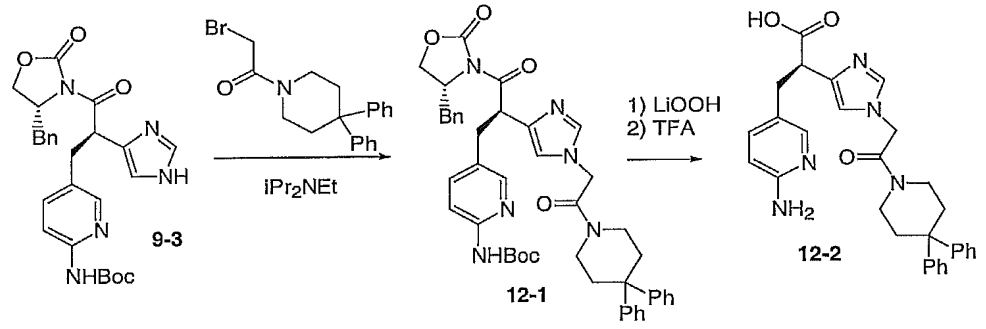


11-15



11-16

Scheme 12



tert-butyl 5-((2*R*)-3-[(4*R*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]-2-{1-[2-(4,4-diphenylpiperidin-1-yl)-2-oxoethyl]-1H-imidazol-4-yl}-3-oxopropyl)pyridin-2-ylcarbamate (**12-1**):

To a solution of tert-butyl 5-[(2R)-3-[(4R)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]-2-(1H-imidazol-4-yl)-3-oxopropyl]pyridin-2-ylcarbamate (**9-3**) (200 mg, 0.41 mmol) in DMF (1.5 mL) was added diisopropylethyl amine (113 µL, 0.65 mmol) and 1-(bromoacetyl)-4,4-diphenylpiperidine (204 mg, 0.57 mmol, prepared from 4,4-diphenyl-piperidine and bromoacetyl bromide) in DMF (0.2 mL). The

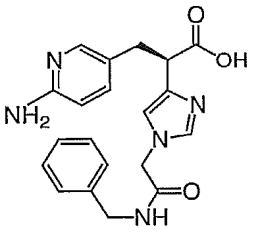
reaction mixture was stirred at room temperature for 20 h. Aqueous LiCl was added and the reaction mixture extracted twice with ethyl acetate. The combined organic layers were dried over sodium sulfate, concentrated in vacuo, and purified by flash chromatography (silica gel, 90 g, 2% to 6% MeOH containing 10% NH_4OH in dichloromethane) to give tert-butyl 5-((2R)-3-[(4R)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]-2-{1-[2-(4,4-diphenylpiperidin-1-yl)-2-oxoethyl]-1H-imidazol-4-yl}-3-oxopropyl)pyridin-2-ylcarbamate (**12-1**) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.08 (d, 1H, , J = 2.5 Hz); 7.79 (d, 1H, , J = 8.8 Hz); 7.53 (dd, 1H, J = 8.8, 2.5 Hz); 7.45 (s, 1H); 7.38-7.13 (m, 15H); 7.04 (d, 2H, , J = 7.5 Hz); 6.81 (s, 1H); 5.31 (s, 2H); 5.30 (t, 1H, J = 7.3 Hz); 4.67 (s, 2H); 4.65-4.55 (m, 1H); 4.05-3.95 (m, 2H); 3.78-3.58 (m, 2H); 3.50-3.38 (m, 3H); 3.23-3.10 (m, 2H); 2.63 (dd, 1H, J = 13.6, 9.9 Hz); 2.45-2.30 (m, 4H); 1.50 (s, 9H).Electrospray Mass Spectrum M+H=769.7.

(2*R*)-3-(6-aminopyridin-3-yl)-2-{1-[2-(4,4-diphenylpiperidin-1-yl)-2-oxoethyl]-1H-imidazol-4-yl}propanoic acid (**12-2**):

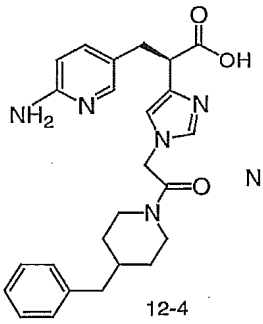
To a solution of methyl tert-butyl 5-((2R)-3-[(4R)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]-2-{1-[2-(4,4-diphenylpiperidin-1-yl)-2-oxoethyl]-1H-imidazol-4-yl}-3-oxopropyl)pyridin-2-ylcarbamate (**12-1**) (110 mg, 0.14 mmol) in THF (4 mL) was added a solution of 1N LiOH (172 μL, 0.172 mmol) and 30% hydrogen peroxide (19 μL, 0.172 mmol) and the reaction mixture stirred at room temperature for 1 h. Addition of ca. A third of the original amount of $LiOH/H_2O_2$ resulted in reaction completion after 15 min. 1N Na_2SO_3 (257 μL, 0.26 mmol) and 1N HCl (257 μL, 0.26 mmol) were added and the THF was removed under a nitrogen stream. The residual aqueous solution was purified by reverse phase preparative HPLC (20x150 mm YMC C18 PRO, 5% to 95% aqueous CH_3CN containing 0.1% TFA, multiple injections) to provide (2R)-3-{6-[(tert-butoxycarbonyl)amino]pyridin-3-yl}-2-{1-[2-(4,4-diphenylpiperidin-1-yl)-2-oxoethyl]-1H-imidazol-4-yl}propanoic acid which was treated with 5 mL TFA at room temperature for 1 h to give (2R)-3-(6-aminopyridin-3-yl)-2-{1-[2-(4,4-diphenylpiperidin-1-yl)-2-oxoethyl]-1H-imidazol-4-yl}propanoic acid bis TFA salt after concentration in vacuo. Elution through a Varian Mega Bond Elut SCX cartridge (1:1 CH_3CN:H_2O, CH_3CN, MeOH/NH_3) afforded (2R)-3-(6-aminopyridin-3-yl)-2-{1-[2-(4,4-diphenylpiperidin-1-yl)-2-oxoethyl]-1H-imidazol-4-yl}propanoic acid (**12-2**) as a white solid.^{1}H NMR ($CDCl_3$ + CD_3OD, 400 MHz): δ 7.73 (d, 1H, , J = 2.1 Hz); 7.49 (br s, 1H); 7.46-7.10 (m, 11H); 6.85 (s, 1H); 6.50 (d, 1H, , J = 8.9 Hz); 4.81 (s, 2H); 3.74 (dd, 1H, , J = 9.4, 6 Hz); 3.72-3.65 (m, 2H); 3.58-

3.52 (m, 2H); 3.12 (A of ABX, dd, 1H, J = 14, 9.4 Hz); 2.98 (B of ABX, dd, 1H, J = 14, 5.9 Hz); 2.53-2.41 (m, 4H). Electrospray Mass Spectrum M+H=510.3.

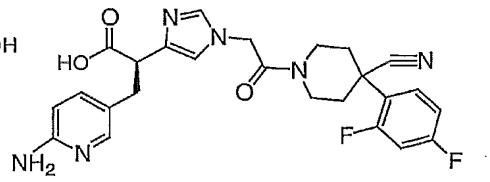
#		name	Mass spec
12-3		(2*R*)-3-(6-aminopyridin-3-yl)-2-{1-[2-(benzylamino)-2-oxoethyl]-1H-imidazol-4-yl}propanoic acid	380
12-4		(2*R*)-3-(6-aminopyridin-3-yl)-2-{1-[2-(4-benzylpiperidin-1-yl)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid	448
12-5		(2*R*)-3-(6-aminopyridin-3-yl)-2-(1-{2-[4-cyano-4-(2,4-difluorophenyl) piperidin-1-yl]-2-oxoethyl}-1*H*-imidazol-4-yl)propanoic acid	495
12-6		(2*R*)-3-(6-aminopyridin-3-yl)-2-(1-{2-oxo-2-[4-(2-phenylethyl)piperidin-1-yl]ethyl}-1*H*-imidazol-4-yl)propanoic acid	462
12-7		(2*R*)-3-(6-aminopyridin-3-yl)-2-{1-[2-(4-*tert*-butylphenyl)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid	407



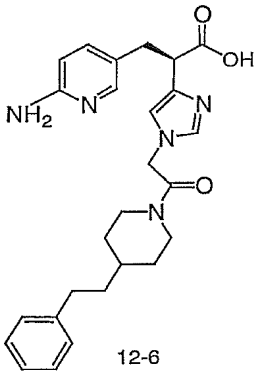
12-3



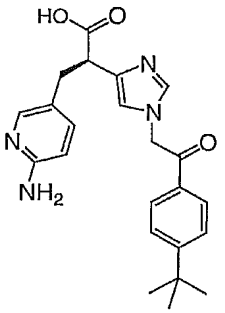
12-4



12-5

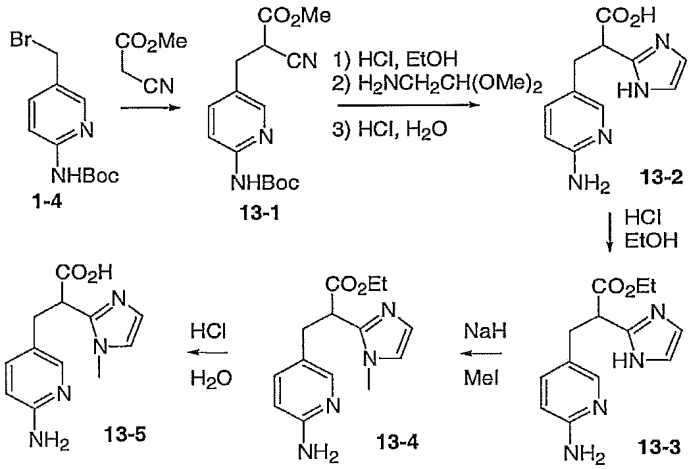


12-6



12-7

Scheme 13



methyl 3-{6-[(*tert*-butoxycarbonyl)amino]pyridin-3-yl}-2-cyanopropanoate (**13-1**)

To a 0 °C suspension of 0.04g (1 mmol, 60% dispersion in mineral oil) sodium hydride was added 0.18 mL (2 mmol) methyl cyanoacetate. After the gas evolution had ceased (30 minutes) 0.1g (0.3 mmol) *tert*-butyl 5-(bromomethyl)pyridin-2-ylcarbamate was added as a solid. After stirring 30 minutes at 0 °C the reaction mixture was diluted with 50 mL EtOAc, washed with 50 mL each of saturated aqueous ammonium chloride, water, and brine, then dried over Na_2SO_4, filtered, and concentrated. Purification by automated flash chromatography (40g silica cartridge, linear gradient 10-60% EtOAc/hexane over 20 min, 40 mL/min flow rate.) afforded methyl 3-{6-[(*tert*-butoxycarbonyl)amino]pyridin-3-yl}-2-cyanopropanoate (**13-1**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, 1H, *J*=2.29 Hz); 7.94 (d, 1H, *J*=8.61 Hz); 7.70 (br s, 1H); 7.60 (dd, 1H, *J*=2.38 and 8.70 Hz); 3.80 (s, 3H); 3.72 (dd, 1H, *J*=5.95 and 7.51 Hz); 3.19 (m, 2H); 1.54 (s, 9H). Electrospray mass spectrum M+Na=328.1

3-(6-aminopyridin-3-yl)-2-(1*H*-imidazol-2-yl)propanoic acid di-trifluoroacetate (**13-2**)

Through a -78 °C solution of 0.05 g (0.16 mmol) methyl 3-{6-[(*tert*-butoxycarbonyl)amino]pyridin-3-yl}-2-cyanopropanoate in 7 mL absolute ethanol was slowly passed HCl gas for 3 minutes. The reaction mixture was stirred 30 minutes at –78 °C, then more HCl gas was passed through the solution for 2 more minutes, then the reaction mixture was warmed to 0 °C for 2 hours, then concentrated. Added 10 mL ether and concentrated to a foam. The residue was then dissolved in 1 mL ethanol and 0.05 mL (0.36 mmol) aminoacetaldehyde diethyl acetal was added and the reaction mixture was stirred at room temperature for 2 hours, then concentrated. The residue was dissolved in 3 mL water and 3 mL concentrated aqueous HCl was added and the reaction mixture heated to 90 °C for 2 hours, then cooled and concentrated. Purification by preparative reverse phase HPLC (20x150 mm C18 column, 0-95% CH_3CN/H_2O (0.1%TFA) over 25 minutes) provided 3-(6-aminopyridin-3-yl)-2-(1*H*-imidazol-2-yl)propanoic acid (**13-2**) as its di-trifluoroacetate salt. ^{1}H NMR (400 MHz, DMSO d_6) δ 8.00 (br s, 2H); 7.74 (s, 1H); 7.70 (dd, 1H, *J*=1.65 and 8.97 Hz); 7.61 (s, 2H); 6.89 (d, 1H, *J*=9.15 Hz); 4.55 (dd, 1H, *J*=6.41 and 9.71 Hz); 3.34 (dd, 1H, *J*=6.23 and 14.3 Hz); 3.23 (dd, 1H, *J*=9.71 and 14.3 Hz) Electrospray mass spectrum M+H=233.1

ethyl 3-(6-aminopyridin-3-yl)-2-(1H-imidazol-2-yl)propanoate (**13-3**)

To a solution of 0.103g (0.224 mmol) 3-(6-aminopyridin-3-yl)-2-(1*H*-imidazol-2-yl)propanoic acid di-trifluoroacetate in 3 mL absolute ethanol was added 1.34 mL (0.134 mmol) of a 1.0M HCl in ether solution and the reaction stirred 24 hours at room temperature. After concentration to dryness, the residue was treated with saturated aqueous sodium bicarbonate and extracted with EtOAc (3x). The extracts were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated to give a crude oil. Flash chromatography on silica gel (160/10/1 of methylene chloride/methanol/concentrated ammonium hydroxide) gave 44 mg of ethyl 3-(6-aminopyridin-3-yl)-2-(1H-imidazol-2-yl)propanoate (**13-3**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (br s, 1H); 7.70 (s, 1H); 7.00 (br m, 3H); 6.37 (d, 1H, *J*=8.43 Hz); 4.37 (br s, 2H); 4.15 (m, 3H); 3.18 (d, 2H, *J*=6.95 Hz); 1.21 (t, 3H, *J*=7.14 Hz) Electrospray mass spectrum M+H=261.2

ethyl 3-(6-aminopyridin-3-yl)-2-(1-methyl-1H-imidazol-2-yl)propanoate ditrifluoroacetate (**13-4**)

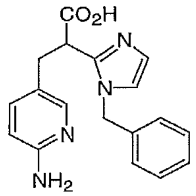
To a 300 uL DMF solution of 21.0 mg (0.081 mmol) ethyl 3-(6-aminopyridin-3-yl)-2-(1H-imidazol-2-yl)propanoate at 0 °C was added 3.9mg (0.1 mmol, 60% dispersion in mineral oil) sodium hydride. After stirring 10 minutes, 5.3 uL (0.085 mmol) of methyliodide was added (neat) and the reaction stirred 30 minutes in the cold. After adding 60 uL water, the reaction mixture was filtered and purified by preparative reverse phase HPLC (20x150 mm C18 column, 0-95% CH_3CN/H_2O (0.1%TFA) over 25 minutes) to give 16.3mg of ethyl 3-(6-aminopyridin-3-yl)-2-(1-methyl-1H-imidazol-2-yl)propanoate (**13-4**) as its di-trifluoroacetate salt. ^{1}H NMR (400 MHz, DMSO d_6) δ 8.03 (br s, 1H); 7.76 (m, 2H); 7.61 (m, 2H); 6.90 (d, 1H, *J*=9.62 Hz); 4.80 (t, 1H, *J*=7.60 Hz); 3.76 (s, 3H); 3.35 (dd, 1H, *J*=7.29 and 14.06 Hz); 3.21 (dd, 1H, *J*=7.92 and 14.15 Hz); 1.15 (t, 3H, *J*=7.10 Hz) Electrospray mass spectrum M+H=275.3

3-(6-aminopyridin-3-yl)-2-(1-methyl-1H-imidazol-2-yl)propanoic acid di-trifluoroacetate (**13-5**)

To 600 ul aqueous 6N HCl was added 12.0 mg (0.024 mmol) of ethyl 3-(6-aminopyridin-3-yl)-2-(1-methyl-1H-imidazol-2-yl)propanoate as its di-trifluoroacetate salt and the resulting solution stirred 24 hours at room temperature.

The reaction was concentrated to dryness, redissolved in 250 uL water and purified by preparative reverse phase HPLC (20x150 mm C18 column, 0-95% CH_3CN/H_2O (0.1%TFA) over 25 minutes) to give 6.9mg of 3-(6-aminopyridin-3-yl)-2-(1-methyl-1H-imidazol-2-yl)propanoic acid (**13-5**) as its di-trifluoroacetate salt. ^1H NMR (400 MHz, DMSO d_6) δ 8.02 (br s, 1H); 7.77 (m, 2H); 7.62 (m, 2H); 6.90 (d, 1H, *J*=9.53 Hz); 4.78 (t, 1H, *J*=7.79 Hz); 3.77 (s, 3H); 3.35 (dd, 1H, *J*=6.87 and 14.38 Hz); 3.25 (dd, 1H, *J*=8.70 and 14.37 Hz). Electrospray mass spectrum M+H=247.1

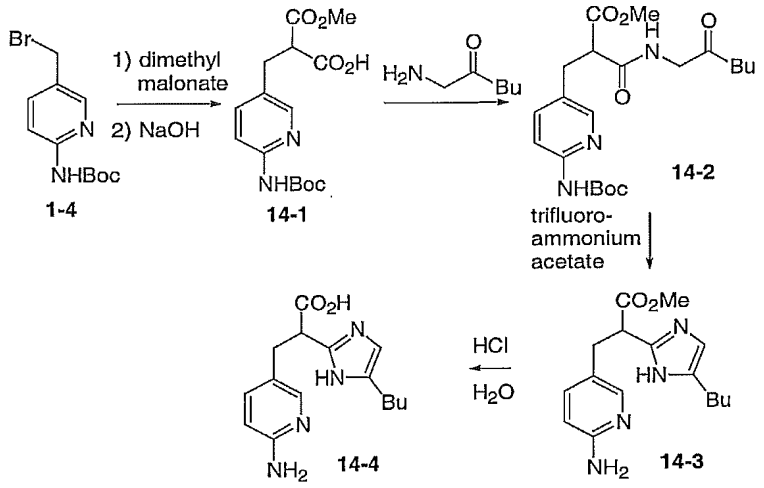
3-(6-aminopyridin-3-yl)-2-(1-benzyl-1H-imidazol-2-yl)propanoic acid di-trifluoroacetate (**13-6**)



13-6

3-(6-aminopyridin-3-yl)-2-(1-benzyl-1H-imidazol-2-yl)propanoic acid (**13-6**) as its di-trifluoroacetate salt was prepared from ethyl 3-(6-aminopyridin-3-yl)-2-(1H-imidazol-2-yl)propanoate (**13-3**) using the two reaction sequence that resulted in (**13-5**) except benzylbromide was substituted for methyliodide in the first step. Electrospray mass spectrum M+H=323.3

Scheme 14



2-(6-*tert*-butoxycarbonylamino-pyridin-3-ylmethyl)-malonic acid monomethyl ester (**14-1**)

To a suspension of sodium hydride (0.54g, 60% dispersion in mineral oil, 22 mmol) in THF (65 mL) at 0° C was added dimethylmalonate (4.6g, 3.98 mL, 34 mmol) *via* syringe. After the gas evolution had ceased (10 minutes) *tert*-butyl-5-(bromomethyl)pyridine-2-ylcarbamate (5.00g, 17.4 mmol) was added portion wise as a solid. After stirring 4 hours at 0 °C the reaction mixture was diluted with 300mL EtOAc, washed with 50 mL each of saturated aqueous sodium bicarbonate, water, and brine, then dried over Na_2SO_4, filtered and concentrated. Purification by automated flash chromatography (120g silica cartridge, linear gradient 5-60% EtOAc/hexane over 30 minutes, 90 mL/min flow rate.) afforded 2-(6-*tert*-butoxycarbonylamino-pyridin-3-ylmethyl)-malonic acid dimethyl ester. ^{1}H NMR (400 MHz, CDCl3) δ 8.09 (s, 1H); 7.84 (d, 1H, *J*=1.8 Hz); 7.5 (d, 1H, *J*=1.8 Hz); 7.18 (s, 1H); 3.7 (s, 6H); 3.6 (t, 1H, *J*=1.6 Hz); 3.14 (d, 2H, *J*=1.6 Hz); 1.54 (s, 9H). Electrospray mass spectrum M+H=339.2

To a suspension of 2-(6-*tert*-butoxycarbonylamino-pyridin-3-ylmethyl)-malonic acid dimethyl ester (0.15g, 0.44 mmol) in dioxane (2mL) was added aqueous 1N NaOH (0.49mL) in solution *via* syringe. After stirring for 24 hours, aqueous 1N HCl (0.49mL) was added *via* syringe. Concentrating the mixture afforded 2-(6-*tert*-butoxycarbonylamino-pyridin-3-ylmethyl)-malonic acid

monomethyl ester (**14-1**). ^{1}H NMR (400 MHz, CD3OD) δ 8.28 (d, 1H, *J*=1.8 Hz); 8.20 (s, 1H); 7.32 (d, 1H, *J*=1.8 Hz); 3.82 (t, 1H, *J*=1.5 Hz); 3.66 (s, 3H) 3.24 (d, 2H, *J*=1.5 Hz); 1.58 (s, 9H). electrospray mass spectrum M+H=325.0

methyl 2-({6-[(*tert*-butoxycarbonyl)amino]pyridin-3-yl}methyl)-3-oxo-3-[(2-oxohexyl)amino]propanoate (**14-2**).

To a solution of 1.0g (4.58 mmol) N-(*tert*-butoxycarbonyl)glycine N′-methoxy-N′-methylamide in 14 mL THF at –78 °C was added 4.12 mL (10.31 mmol) of a 2.5M n-butyl lithium solution in hexane. After stirring 45 minutes at –78 °C, the reaction was treated with saturated aqueous ammonium chloride and extracted with EtOAc (3x). The organic extracts were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated to give 1.06g of a crude colorless oil. Purification by automated flash chromatography (90g silica cartridge, linear gradient 0-100% EtOAc/hexane over 25 min, 60 mL/min flow rate.) gave 0.254g of *tert*-butyl 2-oxohexylcarbamate. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (br s, 1H); 4.01 (d, 2H, *J*=4.39 Hz); 2.42 (t, 2H, *J*=7.51 Hz); 1.60 (m, 2H); 1.45 (s, 9H); 1.32 (m, 2H); 0.91 (t, 3H, *J*=7.33). Electrospray mass spectrum M+Na=238.1

Into a 1.5 mL EtOAc solution at 0 °C containing 0.200g (0.929 mmol) *tert*-butyl 2-oxohexylcarbamate was bubbled $HCl_{(g)}$ until saturated. The reaction was stirred 45 minutes at 0 °C, then concentrated to dryness to give 138mg of 1-amino-2-oxoamine as its hydrochloride salt. ^{1}H NMR (400 MHz, CD_3OD) δ 3.94 (s, 2H); 2.55 (t, 2H, *J*=7.37 Hz); 1.61 (m, 2H); 1.36 (m, 2H); 0.93 (t, 3H, *J*=7.33 Hz).

To a solution of 0.275g (0.848 mmol) 2-(6-*tert*-butoxycarbonylamino-pyridin-3-ylmethyl)-malonic acid monomethyl ester in 6.0 mL DMF was added 0.244g (1.27 mmol) EDC, 0.139g (1.02 mmol) HOAT, 0.142 mL (1.02 mmol) TEA and 0.129g (0.848 mmol) of 1-amino-2-oxoamine as its hydrochloride salt. After stirring at room temperature for 18 hours, the reaction was quenched with water and extracted with EtOAc (3x). The organic extracts were combined, washed with water (1x), brine (1x), dried over Na_2SO_4, filtered and concentrated to give 537mg of a crude yellow oil. Purification by automated flash chromatography (40g silica cartridge, linear gradient 0-100% EtOAc/hexane over 25 min, 40 mL/min flow rate) gave 0.210g of methyl 2-({6-[(*tert*-butoxycarbonyl)amino]pyridin-3-yl}methyl)-3-oxo-3-[(2-oxohexyl)amino] propanoate (**14-2**) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, 1H, *J*=2.10 Hz); 7.83 (d, 1H, *J*=8.61 Hz); 7.49 (dd, 1H, *J*=2.15 and

8.65 Hz); 7.18 (s, 1H); 6.97 (br t, 1H, *J*=5.11 Hz); 4.15 (dd, 1H, *J*=5.08 and 19.8 Hz); 4.08 (dd, 1H, *J*=5.08 and 19.8 Hz); 3.70 (s, 3H); 3.20 (dd, 1H, *J*=7.44 and 14.1 Hz); 2.43 (t, 2H, *J*=7.46 Hz); 1.60 (m, 2H); 1.52 (s, 9H); 1.32 (m, 2H); 0.91 (t, 3H, *J*=7.32). Electrospray mass spectrum M+H=422.1

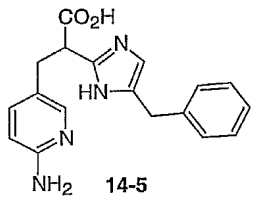
methyl 3-(6-aminopyridin-3-yl)-2-(5-butyl-1H-imidazol-2-yl)propanoate di-trifluoroacetate (**14-3**)

Combined 0.100g (0.237 mmol) of methyl 2-({6-[(tert-butoxycarbonyl)amino]pyridin-3-yl}methyl)-3-oxo-3-[(2-oxohexyl)amino]propanoate and 0.311g ammonium trifluoroacetate, and heated to a molt at 140 °C for 2 hours. Cooled, treated with saturated aqueous sodium bicarbonate and extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. Purification by preparative reverse phase HPLC (20x150 mm C18 column, 0-95% CH_3CN/H_2O (0.1%TFA) over 25 minutes) gave 23.2mg of methyl 3-(6-aminopyridin-3-yl)-2-(5-butyl-1H-imidazol-2-yl)propanoate (**14-3**) as its di-trifluoroacetate salt. ^{1}H NMR (400 MHz, CD_3OD) δ 7.73 (dd, 1H, *J*=2.20 and 9.34 Hz); 7.65 (d, 1H, *J*=1.65 Hz); 7.27 (s, 1H); 6.96 (d, 1H, *J*=9.34); 4.49 (t, 1H, *J*=7.88 Hz); 3.78 (s, 3H); 3.43 (dd, 1H, *J*=7.14 and 14.29 Hz); 3.20 (dd, 1H, *J*=8.15 and 14.29 Hz); 2.43 (t, 2H, *J*=7.46 Hz); 1.60 (m, 2H); 1.56 (s, 9H); 1.32 (m, 2H); 0.91 (t, 3H, *J*=7.32). electrospray mass spectrum M+H=422.1

3-(6-aminopyridin-3-yl)-2-(5-butyl-1H-imidazol-2-yl)propanoic acid di-trifluoraoacetate (**14-4**)

Dissolved 23mg (0.043 mmol) of methyl 3-(6-aminopyridin-3-yl)-2-(5-butyl-1H-imidazol-2-yl)propanoate as its di-trifluoroacetate salt in 1.2 mL aqueous 6N HCl and stirred 18 hours at room temperature. Concentrated to remove solvent, redissolved residue in 400 uL water and purified by preparative reverse phase HPLC (20x150 mm C18 column, 0-95% CH_3CN/H_2O (0.1%TFA) over 25 minutes) to give 14.1mg of 3-(6-aminopyridin-3-yl)-2-(5-butyl-1H-imidazol-2-yl)propanoic acid (**14-4**) as its di-trifluoroacetate salt. ^{1}H NMR (400 MHz, DMSO d_6) δ 8.07 (br s, 1H); 7.66 (m, 1H); 7.35 (s, 1H); 6.88 (d, 1H, *J*=8.97); 4.43 (dd, 1H, *J*=6.23 and 9.71 Hz); 3.33 (dd, 1H, *J*=6.32 and 14.1 Hz); 3.13 (dd, 1H, *J*=9.70 and 14.0 Hz); 2.58 (t, 2H, *J*=7.33 Hz); 1.53 (m, 2H); 1.25 (m, 2H); 0.87 (t, 3H, *J*=7.32). Electrospray mass spectrum M+H=289.1

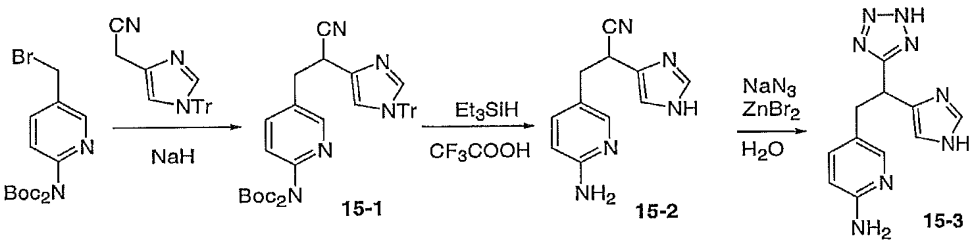
3-(6-aminopyridin-3-yl)-2-(5-benzyl-1H-imidazol-2-yl)propanoic acid difluoroacetate (**14-5**)



14-5

3-(6-aminopyridin-3-yl)-2-(5-benzyl-1H-imidazol-2-yl)propanoic acid as its di trifluoroacetate salt (**14-5**) was prepared from 2-(6-*tert*-butoxycarbonylamino-pyridin-3-ylmethyl)-malonic acid monomethyl ester (**14-1**) using the same multistep sequence that gave 3-(6-aminopyridin-3-yl)-2-(5-butyl-1H-imidazol-2-yl)propanoic acid di-trifluoraoacetate (**14-4**) except benzylmagnesium chloride was substituted for butyllithium in the first step to react with N-(*tert*-butoxycarbonyl)glycine N′-methoxy-N′-methylamide at 0 °C. Electrospray mass spectrum M+H=323.3

Scheme 15



di(*tert*-butyl) 5-[2-cyano-2-(1-trityl-1H-imidazol-4-yl)ethyl]pyridin-2-ylimidodicarbonate (**15-1**)

To a solution of 0.30 mL (2.16 mmol) diisopropylamine in 1.5 mL THF at –78 °C was added dropwise 0.87 mL (2.16 mmol) of a 2.5M n-buLi solution in hexane. The solution was stirred at –78 °C for 30 minutes, warmed to 0 °C for 20 minutes, and recooled to –78 °C followed by a dropwise addition of a 7 mL THF solution of 0.687g (1.97 mmol) (1-trityl-1H-imidazol-4-yl)acetonitrile (J. Med. Chem., 1977, Vol. 20, p 1671-4). The mixture was stirred at –78 C for 30 minutes and to this was added a 6 mL THF solution of 0.647g (1.67 mmol) di(*tert*-butyl) 5-(bromomethyl)pyridin-2-ylimidodicarbonate (prepared from (**1-3**) by silylation with *tert*butyl dimethylsilyl chloride, installation of the second boc with Boc_2O and DMAP, desilylation with tetrabutyl ammonium fluoride, and bromination via the

procedure for **1-4**). After 1 hour at –78 °C, the reaction was quenched with saturated aqueous ammonium chloride and extracted with EtOAc (3x). The organic extracts were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness to give 1.09g of a crude oil. Purification by automated flash chromatography (40g silica cartridge, linear gradient 0-80% EtOAc/hexane over 20 min, 40 mL/min flow rate) gave 677mg of an oil which required further purification. Rechromatography (40g silica cartridge, linear gradient 7-15% acetone/methylene chloride over 25 min, 40 mL/min flow rate.) gave 450mg of di(*tert*-butyl) 5-[2-cyano-2-(1-trityl-1H-imidazol-4-yl)ethyl]pyridin-2-ylimidodicarbonate (**15-1**) as an oil. ^1H NMR (400 MHz, DMSO d_6) δ 8.26 (d, 1H, *J*=2.2 Hz); 7.55 (dd, 1H, *J*=1.8 and 8.2 Hz); 7.47 (m, 1H); 7.34 (m, 9H); 7.18 (d, 1H, *J*=8.2 Hz); 7.08 (m, 6H); 6.71 (s, 1H); 4.09 (m, 1H); 3.30 (m, 1H); 1.41 (s, 9H). electrospray mass spectrum M+Na=678.3

3-(6-aminopyridin-3-yl)-2-(1H-imidazol-4-yl)propanenitrile (**15-2**)

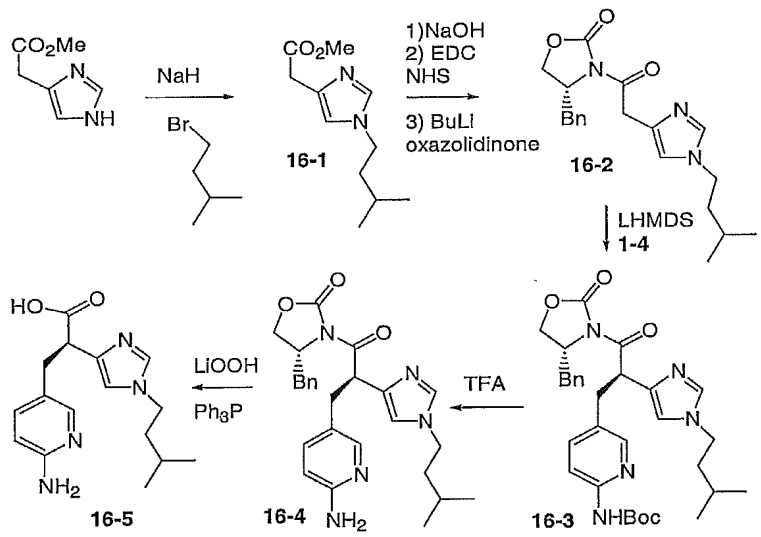
To a solution of 0.225g (0.343 mmol) di(*tert*-butyl) 5-[2-cyano-2-(1-trityl-1H-imidazol-4-yl)ethyl]pyridin-2-ylimidodicarbonate in 1.5 mL methylene chloride was added 70 uL (0.412 mmol) triethylsilane and 130 uL (1.72 mmol) trifluoroacetic acid. The reaction was stirred overnight at room temperature, then 0.5 mL methylene chloride and 130 uL (1.72 mmol) trifluoroacetic acid were added and the reaction stirred at reflux for 3 hours. The reaction was concentrated to dryness, treated with 3.0 mL water and extracted with diethyl ether (2x). The acidic water phase was then loaded onto a Varian Bond Elut SCX ion exchange (sulfonic acid) column (pretreated with 1:1 CH3CN:H_2O). Washed column with 5 mL CH_3CN followed by MeOH containing 5% NH_3. Concentration of the product fractions gave 66.3mg of 3-(6-aminopyridin-3-yl)-2-(1H-imidazol-4-yl)propanenitrile (**15-2**) as an oil. ^1H NMR (400 MHz, CD_3OD) δ 7.71 (s, 1H); 7.66 (d, 1H, *J*= 2.2 Hz); 7.30 (dd, 1H, *J*=2.3 and 8.4 Hz); 6.98 (s, 1H); 6.50 (d, 1H, *J*=8.6 Hz); 4.21 (br t, 1H, *J*=7.2 Hz); 3.10 (m, 2H). electrospray mass spectrum M+H=214.1

5-[2-(1H-imidazol-4-yl)-2-(2H-tetraazol-5-yl)ethyl]pyridin-2-amine di-trifluoroacetate (**15-3**)

To a solution of 32.5mg (0.152 mmol) 3-(6-aminopyridin-3-yl)-2-(1H-imidazol-4-yl)propanenitrile in 300 uL H2O was added 10.4mg (0.160 mmol) NaN_3 and 17.1mg (0.076 mmol) zinc bromide. The reaction mixture was stirred vigorously

at 100 °C for 48 hours. The reaction mixture was cooled, dissolved by adding 1.2 mL aqueous 0.5N HCl and purifying by preparative reverse phase HPLC (20x150 mm C18 column, 0-95% CH_3CN/H_2O (0.1%TFA) over 25 minutes) to give 13.3mg of 5-[2-(1H-imidazol-4-yl)-2-(2H-tetraazol-5-yl)ethyl]pyridin-2-amine (**15-3**) as its ditrifluoroacetate salt. ^{1}H NMR (400 MHz, DMSO d_6) δ 8.61 (s, 1H); 7.75 (br s, 1H); 7.67 (s, 1H); 7.62 (d, 1H, *J*=9.2 Hz); 7.41 (s, 1H); 6.82 (d, 1H, *J*=9.1 Hz); 4.87 (t, 1H, *J*=7.8 Hz); 3.32 (d, 2H, *J*=7.8 Hz). electrospray mass spectrum M+H=257.1

Scheme 16



methyl (1-isopentyl-1*H*-imidazol-4-yl)acetate (**16-1**)

To a 0 °C solution of 15g (85 mmol) methyl 4-imidazole acetate hydrochloride in 150 mL DMF was slowly added 7.5g (187 mmol, 60% dispersion in mineral oil) NaH. The reaction mixture was stirred for 2 hours at 0 °C then cooled to –78 °C whereupon 10 mL (85 mmol) *iso*pentyl bromide was added and the reaction mixture was allowed to warm to room temperature and stir an additional 2 hours. The resulting mixture was concentrated to 1/3 volume then partitioned between 700 mL EtOAc and 500 mL water. The aqueous layer was extracted again with 200 mL EtOAc and the combined extracts were washed with 700 mL each of dilute brine and brine, dried over Na_2SO_4, filtered and concentrated. Purification by automated flash chromatography (400g silica gel cartridge, 1-6% $MeOH/CH_2Cl_2$ at 200 mL/min) followed by repurification of mixed fractions (300g silica gel cartridge, 1-5%

MeOH/CH_2Cl_2 at 100 mL/min) provided 9g methyl (1-isopentyl-1*H*-imidazol-4-yl)acetate (**16-1**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, 1H, *J*=1.0 Hz); 6.87 (d, 1H, *J*=0.65 Hz); 3.90 (t, 2H, *J*=7.33 Hz); 3.72 (s, 3H); 3.65 (s, 2H); 1.7-1.5 (m, 3H); 0.94 (d, 6H, *J*=6.4 Hz). Electrospray mass spectrum M+H=211.1

(4*R*)-4-benzyl-3-[(1-isopentyl-1*H*-imidazol-4-yl)acetyl]-1,3-oxazolidin-2-one (**16-2**)

To a solution of 8.1g (38.5 mmol) methyl (1-isopentyl-1*H*-imidazol-4-yl)acetate (**16-1**) in 150 mL THF was added 40 mL (40 mmol , 1M aqueous solution) NaOH and the resulting mixture stirred 1 hour then concentrated and resuspended in 200 mL CH_2Cl_2. To this was added 19 mL (38 mmol, 2M solution in ether) HCl, 5.3g (46 mmol) *N*-hydroxysuccinimide, and 10.3g (54 mmol) EDC and the resulting mixture stirred 4 hours then diluted with 400 mL EtOAc, washed with 300 mL dilute sodium carbonate solution, 300 mL water, 300 mL brine, dried over $MgSO_4$, filtered and concentrated to give 1-{[(1-isopentyl-1*H*-imidazol-4-yl)acetyl]oxy}pyrrolidine-2,5-dione which was dissolved in 100 mL THF and cooled to –78 °C. To this was added a –78 °C mixture of 5.9g (33.4 mmol) (*R*) 4-benzyl-2-oxazolidinone and 14 mL (35 mmol, 2.5M solution in hexane) butyllithium in 100 mL THF via cannula. The resulting mixture was allowed to warm slowly with the dry-ice bath and quenched after 2 hours by pouring into a well stirred mixture of 400 mL EtOAc/300 mL water/ 40 mL 1N HCl. The pH was raised to pH=9 by addition of NaOH solution and the layers mixed and separated. The organic layer was washed with 300 mL water, 300 mL brine, dried over Na_2SO_4, filtered, and concentrated. Purification by automated flash chromatography (300g silica gel cartridge, linear gradient 1-3% MeOH/ CH_2Cl_2 over 30 min) followed by repurification of mixed fractions (300g silica gel cartridge, linear gradient 1-3.5% MeOH/ CH_2Cl_2 over 30 min) to give 6.8g (4*R*)-4-benzyl-3-[(1-isopentyl-1*H*-imidazol-4-yl)acetyl]-1,3-oxazolidin-2-one (**16-2**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, 1H, *J*=1.28 Hz); 7.31 (m, 3H); 7.20 (m, 2H); 6.89 (br s, 1H); 4.69 (m, 1H); 4.30 (d, 1H, *J*=16.8 Hz); 4.23 (d, 1H, *J*=17.0 Hz); 4.18 (m, 2H); 3.91 (t, 2H, *J*=7.32 Hz); 3.35 (dd, 1H, *J*=13.4 and 3.30 Hz); 2.76 (dd, 1H, *J*=13.4 and 9.71 Hz); 1.7-1.5 (m, 3H); 0.94 (d, 6H, *J*=6.59 Hz). Electrospray mass spectrum M+H=356.1)

tert-butyl 5-[(2*R*)-3-[(4*R*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]-2-(1-isopentyl-1*H*-imidazol-4-yl)-3-oxopropyl]pyridin-2-ylcarbamate (**16-3**)

To a –78 °C solution of 5g (14 mmol) (4*R*)-4-benzyl-3-[(1-isopentyl-1*H*-imidazol-4-yl)acetyl]-1,3-oxazolidin-2-one (**16-2**) in 100 mL THF was added 15.5

mL (15.5 mmol, 1M solution in THF) LHMDS followed by 4g (14 mmol) *tert*-butyl 5-(bromomethyl)-pyridin-2-ylcarbamate (**1-4**) 15 minutes later. The resulting solution was maintained at –78 °C for 4.5 hours then quenched by pouring into a well stirred mixture of 400 mL EtOAc/300 mL water/15 mL HCl and then the pH raised to pH=9 with NaOH. The organic layer was washed with 300 mL saturated aqueous sodium bicarbonate solution, 300 mL brine, dried over Na_2SO_4, filtered and concentrated. Purification by automated flash chromatography (300g silica gel cartridge, linear gradient 1-5% MeOH/ CH_2Cl_2 @ 100 mL/min over 30 min) afforded 7.5g *tert*-butyl 5-[(2*R*)-3-[(4*R*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]-2-(1-isopentyl-1*H*-imidazol-4-yl)-3-oxopropyl]pyridin-2-ylcarbamate (**16-3**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (δ, 1H, *J*=2.0 Hz); 7.79 (d, 1H, *J*=8.6 Hz); 7.50 (dd, 1H, *J*=2.1 and 8.4 Hz); 7.38 (d, 1H, *J*=1 Hz); 7.28 (m, 3H); 7.08 (m, 2H); 6.73 (d, 1H, *J*=1.1 Hz); 5.26 (t, 1H, *J*=7.7 Hz); 4.65 (m, 1H); 4.07 (m, 2H); 3.83 (t, 2H, *J*=7.5 Hz); 3.41 (dd, 1H, *J*=13.7 and 7.9 Hz); 3.21 (m, 2H); 2.65 (dd, 1H, *J*=13.2 and 9.5 Hz); 1.63-1.5 (m, 3H); 1.53 (s, 9H); 0.91 (d, 3H, *J*=6.6 Hz); 0.90 (d, 3H, *J*=6.5 Hz). Electrospray mass spectrum M+H=562.3

(4*R*)-3-[(2*R*)-3-(6-aminopyridin-3-yl)-2-(1-isopentyl-1*H*-imidazol-4-yl)propanoyl]-4-benzyl-1,3-oxazolidin-2-one (**16-4**)

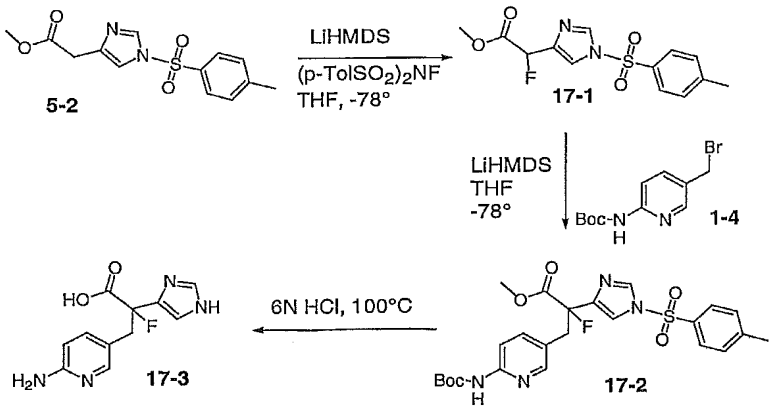
To a 0 °C solution of 7.3g (13 mmol) *tert*-butyl 5-[(2*R*)-3-[(4*R*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]-2-(1-isopentyl-1*H*-imidazol-4-yl)-3-oxopropyl]pyridin-2-ylcarbamate (**16-3**) in 20 mL CH_2Cl_2 was added 100 mL TFA and the mixture was allowed to warm to room temperature and stir for 1.5 hours. To this was added 100 mL toluene and the reaction mixture concentrated, diluted with 400 mL EtOAc, washed w. 100 mL each of saturated sodium bicarbonate solution and brine, then dried over Na_2SO_4, filtered and concentrated. Purification by automated flash chromatography (120g silica gel cartridge, linear gradient 3-8% MeOH/ CH_2Cl_2 @ 90 mL/min over 30 min) followed by repurification of the mixed fractions (120g silica gel cartridge, linear gradient 3-8% MeOH/ CH_2Cl_2 @ 90 mL/min over 30 min) afforded 3.5g (4*R*)-3-[(2*R*)-3-(6-aminopyridin-3-yl)-2-(1-isopentyl-1*H*-imidazol-4-yl)propanoyl]-4-benzyl-1,3-oxazolidin-2-one (**16-4**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, 1H, *J*=2.0 Hz); 7.38 (d, 1H, *J*=1.3 Hz); 7.35 (dd, 1H, *J*=2.3 and 8.4 Hz); 7.26 (m, 3H); 7.08 (m, 2H); 6.77 (d, 1H, *J*=1.3 Hz); 6.41 (d, 1H, *J*=8.2 Hz); 5.28 (t, 1H, *J*=7.9 Hz); 4.65 (m, 1H); 4.07 (d, 2H, *J*=4.9 Hz); 3.85 (t, 2H, *J*=7.3 Hz); 3.35 (dd, 1H, *J*=13.7 and 8.2 Hz); 3.18 (dd, 1H, *J*=13.4 and 3.1 Hz); 3.10 (dd, 1H, *J*=13.7 and

7.3 Hz); 2.64 (dd, 1H, *J*=13.4 and 9.3 Hz); 1.63 (br q, 2H, *J*=7.5 Hz); 1.51 (hept, 1H, *J*=6.8 Hz); 0.92 (d, 3H, *J*=6.6 Hz); 0.91 (d, 3H, *J*=6.60 Hz). Electrospray mass spectrum M+H = 462.3 optical rotation $[\alpha]_D^{24}$= -112° (c=1.0 in CH_2Cl_2)

(2*R*)-3-(6-aminopyridin-3-yl)-2-(1-isopentyl-1*H*-imidazol-4-yl)propanoic acid (**16-5**)

To a solution of 0.6g (1.3 mmol) (4*R*)-3-[(2*R*)-3-(6-aminopyridin-3-yl)-2-(1-isopentyl-1*H*-imidazol-4-yl)propanoyl]-4-benzyl-1,3-oxazolidin-2-one (**16-4**) in 10 mL THF was added 0.5g (1.95 mmol) triphenylphosphine followed by a mixture of 1.43 mL (1.43 mmol, 1M aqueous solution) lithium hydroxide and 0.2 mL (1.95 mmol, 30% wt solution in water) hydrogen peroxide. After 2 hours the mixture was brought to pH=3 by addition of 1.7 mL (1.7 mmol, 1M aqueous solution) HCl and then loaded on a 6g Oasis® MCX ion exchange (sulfonic acid) column (pretreated with 1:1 CH_3CN:H_2O). Washed with 40 mL CH_3CN then eluted product with 3% NH_3/MeOH and concentrated. The residue was triturated from EtOAc to provide 0.2g (2*R*)-3-(6-aminopyridin-3-yl)-2-(1-isopentyl-1*H*-imidazol-4-yl)propanoic acid (**16-5**) as a white solid.). ^{1}H NMR (400 MHz, $DMSOd_6$) δ 7.64 (d, 1H, *J*=2.0 Hz); 7.49 (d, 1H, *J*=1.3 Hz); 7.11 (dd, 1H, *J*=2.4 and 8.4 Hz); 6.86 (br s, 1H); 6.28 (d, 1H, *J*=8.4 Hz); 5.57 (br m, 2H); 3.88 (t, 2H, *J*=7.1 Hz); 3.42 (t, 1H, *J*=7.7 Hz); 2.90 (dd, 1H, *J*=13.7 and 8.2 Hz); 2.75 (dd, 1H, *J*=13.7 and 6.8 Hz); 1.63 (br q, 2H, *J*=7.7 Hz); 1.51 (hept, 1H, *J*=6.8 Hz); 0.88 (d, 3H, *J*=6.6 Hz); 0.87 (d, 3H, *J*=6.6 Hz). Electrospray mass spectrum M+H=303.1 optical rotation $[\alpha]_D^{24}$= -29° (c=0.41 in H_2O).

Scheme 17



Methyl fluoro{1-[(4-methylphenyl)sulfonyl]-1*H*-imidazol-4-yl}acetate (**17-1**)

To a solution of methyl {1-[(4-methylphenyl)sulfonyl]-1*H*-imidazol-4-yl}acetate (500 mg. 1.7 mmol) in THF at -78° C was added LiHMDS (1.7 mL of a 1M solution in THF, 1.7 mmol)via syringe and the reaction stirred at -78° C for 5 min. N-fluoro-p-toluene sulfinamide (535 mg, 1.7 mmol)was then added and the reaction warmed slowly to room temperature following by LC/MS. After 15 minutes at room temperature the reaction was poured into saturated sodium bicarbonate (100 mL), extracted with ethyl acetate (3X50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated at reduced pressure. The residue was chromatographed on silica gel eluting with 10-25% ethyl acetate/methylene chloride to give 345 mg of methyl fluoro{1-[(4-methylphenyl) sulfonyl]-1*H*-imidazol-4-yl}acetate (**17-1**).. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.00 (s, 1H), 7.85 (d, J = 8.2 Hz, 2H), 7.45 (d, J = 2.7 Hz, 1H), 7.39 (d, J = 8.2 Hz, 2H), 5.79 (d, J = 48 Hz, 1H), 3.84(s, 3H), 2.46 (s, 3H). Mass Spectrum (electrospray) M+H= 313.

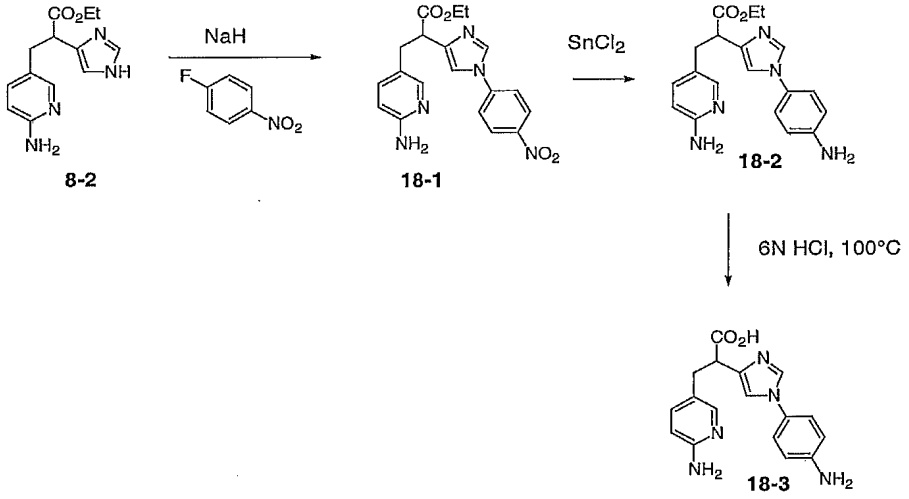
Methyl 3-{6-[(tert-butoxycarbonyl)amino]pyridin-3-yl}-2-fluoro-2-{1-[(4-methylphenyl)sulfonyl]-1H-imidazol-4-yl}propanoate (**17-2**)

To a solution of Methyl fluoro{1-[(4-methylphenyl)sulfonyl]-1*H*-imidazol-4-yl}acetate (312 mg, 1 mmol) in THF at -78° C was added a solution of LiHMDS (1 mL, 1 mmol) via syringe. The reaction was stirred at -78° C for 5 min and then *tert*-butyl 5-(bromomethyl)pyridin-2-ylcarbamate (287 mg, 1 mmol) was added as a solid in one portion. The reaction was allowed to warm to room temperature and poured into a solution of saturated sodium bicarbonate (50 mL) and extracted with ethyl acetate (3X50 mL). The organics were dried over anhydrous sodium sulfate, filtered, and concentrated at reduced pressure . The residue was purified by reverse phase HPLC eluting with 5-95% acetonitrile / water buffered with 0.025% TFA. Fractions with the desired product were then partitioned between saturated sodium bicarbonate solution and ethyl acetate to provide the free base of methyl 3-{6-[(tert-butoxycarbonyl) amino]pyridin-3-yl}-2-fluoro-2-{1-[(4-methylphenyl)sulfonyl]-1H-imidazol-4-yl}propanoate (**17-2**) (40 mg) ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.3 (br s, 1H), 8.3 (d, J = 9.1 Hz, 1H), 8.0 (t, J = 1.5 Hz, 1H), 7.93 (br s, 1H), 7.84 (br d, J = 9 Hz, 1H), 7.81 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 7.35 (br s, 1H), 3.60 (dd, J =20, 15 Hz, 1H), 3.55 (dd, J = 22, 15Hz, 1H), 2.47 (s, 3H), 1.55 (s, 9H). Mass Spectrum (electrospray) M+H= 519.

3-(6-Aminopyridin-3-yl)-2-fluoro-2-(1H-imidazol-4-yl)propanoic acid (**17-3**)

A solution of Methyl 3-{6-[(tert-butoxycarbonyl)amino]pyridin-3-yl}-2-fluoro-2-{1-[(4-methylphenyl)sulfonyl]-1H-imidazol-4-yl}propanoate (40 mg, 0.07 mmol) in 15 mL of 6N HCl was heated to 100° C for 30 minutes , cooled to room temperature, and concentrated at reduced pressure. The material was purified by reverse phase HPLC and the fractions containing the desired product were concentrated at reduced pressure to give 9 mg of 3-(6-aminopyridin-3-yl)-2-fluoro-2-(1H-imidazol-4-yl)propanoic acid (**17-3**) as the bis TFA salt. ^{1}H NMR (D_2O, 400 MHz) δ 8.55 (s, 1H), 7.58 (d, J = 9.2 Hz, 1H), 7.47 (s, 1H), 7.41 (s, 1H), 6.75 (d, J = 9.2 Hz, 1H), 3.35-3.20 (m, 2H). Mass Spectrum (electrospray) M+H=251.

Scheme 18



Ethyl 3-(6-aminopyridin-3-yl)-2-[1-(4-nitrophenyl)-1H-imidazol-4-yl]propanoate (**18-1**).

To a stirred solution of ethyl 3-(6-aminopyridin-3-yl)-2-(1H-imidazol-4-yl)propanoate (**8-2**) (910 mg, 3.50 mmol) in DMF (35.0 ml) cooled to 0°C was added sodium hydride (83.9 mg, 3.50 mmol). The reaction mixture was stirred for 1.25 h, at which time p-fluoronitrobenzene (1.11 mL, 10.49 mmol) was added. The reaction mixture was warmed to room temperature, quenched with aqueous sodium

bicarbonate (100 mL) after 3 h, and extracted repeatedly with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, concentrated in vacuo, and purified by automated flash chromatography (silica gel, 25 g, 0% to 15 % MeOH containing 10%NH_4OH in dichloromethane over 20 min) to give 663 mg of title compound as a yellow solid (50%): ^{1}H NMR (CD_3OD, 400 MHz) δ 8.39 (d, 2H, *J* = 8.8 Hz), 8.31 (s, 1H), 7.83 (d, 2H, *J* = 8.8 Hz), 7.68 (s, 1H), 7.63 (s, 1H), 7.33 (d, 1H, *J* = 8.8 Hz), 6.50 (d, 1H, *J* = 8.4 Hz), 4.11 (m, 2H), 3.93 (t, 1H, *J* = 8.0 Hz), 3.18 (dd, 1H, *J* = 14.0, 8.8 Hz), 3.08 (dd, 1H, *J* = 13.8, 7.4 Hz), 1.17 (t, 3H, *J* = 7.0 Hz); Mass Spectrum (Electrospray, M+H) = 382.6.

Ethyl 2-[1-(4-aminophenyl)-1H-imidazol-4-yl]-3-(6-aminopyridin-3-yl)propanoate (**18-2**)

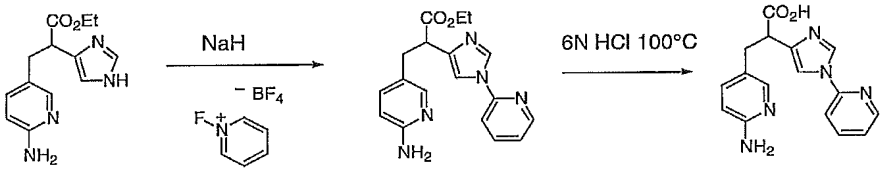
To a stirred solution of ethyl 3-(6-aminopyridin-3-yl)-2-[1-(4-nitrophenyl)-1H-imidazol-4-yl]propanoate (**18-1**) (174 mg, 0.46 mmol) in MeOH was added tin(II) chloride (514 mg, 2.28 mmol). The reaction mixture was stirred at room temperature for 30 min and then warmed to 70°C for 1.5 h. The reaction mixture was concentrated in vacuo to give an orange foam, which was dissolved in aqueous sodium bicarbonate. A yellow precipitate resulted and was removed by filtration. The filtrate was extracted repeatedly with EtOAc (5 x 50 mL), and the combined organics were washed with brine (50 mL), dried over Na2SO4, filtered, and concentrated in vacuo to give 125 mg of title compound as a yellow solid (78%): ^{1}H NMR (CD_3OD, 400 MHz) δ 7.84 (s, 1H), 7.67 (s, 1H), 7.32 (dd, 1H, *J* = 8.4, 2.4 Hz), 7.23 (s, 1H), 7.18 (d, 2H, *J* = 8.8 Hz), 6.77 (d, 2H, *J* = 8.8 Hz), 6.50 (d, 1H, *J* = 8.4 Hz), 4.09 (m, 2H), 3.87 (t, 1H, *J* = 7.8 Hz), 3.14 (dd, 1H, *J* = 14.0, 8.4 Hz), 3.04 (dd, 1H, *J* = 13.8, 7.0 Hz), 1.16 (t, 3 H, *J* = 7.0 Hz); Mass Spectrum (Electrospray, M+H) = 352.6.

2-[1-(4-aminophenyl)-1H-imidazol-4-yl]-3-(6-aminopyridin-3-yl)propanoic acid (**18-3**).

A solution of ethyl 2-[1-(4-aminophenyl)-1H-imidazol-4-yl]-3-(6-aminopyridin-3-yl)propanoate (**18-2**) (31 mg, 0.09 mmol) in 6 N HCl (0.5 mL) was stirred at 100 °C for 1 hour. The reaction was concentrated in vacuo, reconcentrated in vacuo from MeCN, and purified by preparative reverse phase chromatography to give 29.8 mg of title compound as a clear, colorless residue, tris-TFA salt (51%): ^{1}H

NMR (CD_3OD, 400 MHz) δ 9.02 (s, 1H), 7.85 (d, 1H, J = 9.2 Hz), 7.76 (s, 1H), 7.69 (s, 1H), 7.35 (dd, 2H, J = 8.8, 1.6 Hz), 6.96 (d, 1H, J = 9.2), 6.86 (d, 2H, J = 8.4, 1.6 Hz), 4.18 (t, 1H, J = 7.4 Hz), 3.35 (dd, 1H, J = 14.8, 9.2 Hz), 3.15 (dd, 1H, J = 14.0, 7.2); Mass Spectrum (Electrospray, M+H) = 324.6.

Scheme 19



8-2 19-1 19-2

Ethyl 3-(6-aminopyridin-3-yl)-2-(1-pyridin-2-yl-1H-imidazol-4-yl)propanoate (**19-1**).

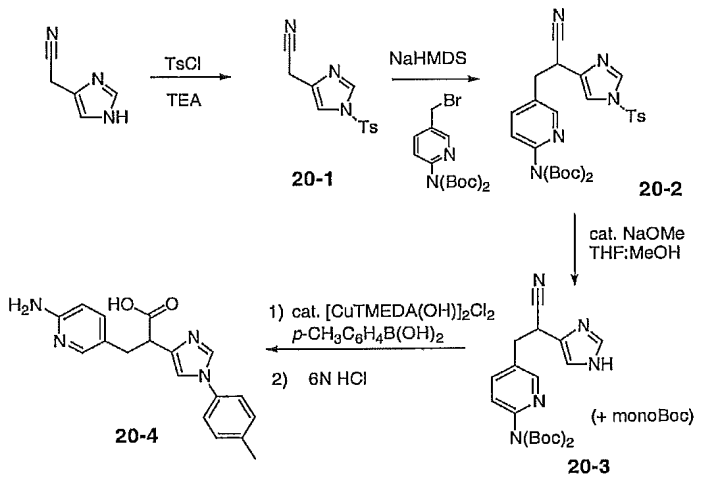
To a stirred solution of ethyl 3-(6-aminopyridin-3-yl)-2-(1H-imidazol-4-yl)propanoate (**8-2**) (61 mg, 0.23 mmol) in EtOH (1.0 mL), was added sodium ethoxide (19 mg, 0.28 mmol). The reaction mixture was stirred at room temperature for 30 min and then cooled to –78°C. 1-fluoropyridinium tetraflouroborate was added portionwise as a solid over a period of 15 min. The reaction mixture was stirred at –78°C for 1 hour and then warmed to room temperature over 1.5 hours. The reaction was quenched with ether (0.5 mL), precipitating the inorganic salts. The salts were subsequently removed by filtration and the filtrate concentrated in vacuo to give 15.0 mg of the ethyl 3-(6-aminopyridin-3-yl)-2-(1-pyridin-2-yl-1H-imidazol-4-yl)propanoate (**19-1**) (19%) which was found to be of sufficient purity for continuation to the next step of the synthesis: Mass Spectrum (Electrospray, M+H) = 338.6.

3-(6-Aminopyridin-3-yl)-2-(1-pyridin-2-yl-1H-imidazol-4-yl)propanoic acid (**19-2**).

A solution of ethyl 3-(6-aminopyridin-3-yl)-2-(1-pyridin-2-yl-1H-imidazol-4-yl)propanoate (**19-1**) (15 mg, 0.04 mmol) in 6 N HCl (0.5 mL) was stirred at 100°C for 1 hour. The reaction was concentrated in vacuo, reconcentrated in vacuo from MeCN, and purified by reverse phase chromatography to give 5.0 mg of title compound as a clear, colorless residue, bis-TFA salt (21%): ^{1}H NMR (CD_3OD, 400 MHz) δ 9.33 (s, 1H), 8.44 (d, 1H, J = 4.4 Hz), 8.00 (t, 1H, J = 7.8 Hz), 7.96 (s, 1H), 7.65 (m, 2H), 7.53 (s, 1H), 7.49 (t, 1H, J = 6.2 Hz), 6.84 (d, 1H, J = 9.2 Hz), 4.18 (t,

1H, J = 7.6 Hz), 3.24 (dd, 1H, J = 14.4, 7.6 Hz), 3.09 (dd, 1H, J = 14.6, 7.8 Hz); Mass Spectrum (Electrospray, M+H) = 310.6.

Scheme 20



{1-[(4-Methylphenyl)sulfonyl]-1H-imidazol-4-yl}acetonitrile (**20-1**)

4-Cyanomethylimidazole (6.0 g, 56 mmol) was suspended in a 200 mL CH_2Cl_2 solution containing triethylamine (7.8 mL, 56 mmol). The reaction mixture was cooled in an ice bath and p-toluenesulfonylchloride (10.7 g, 56 mmol) added as a solid. After 15 min. the ice bath was removed and after 15 additional min. the reaction mixture was diluted with 50 mL CH_2Cl_2 and washed first with a mixture of 50 mL water and 15 mL of sat. NH_4Cl, followed by 100 mL water and finally 40 mL of brine. The CH_2Cl_2 layer was dried over Na_2SO_4, filtered and concentrated. Purification by automated flash chromatography using a 2 to 10% EtOAc/CH_2Cl_2 gradient over 15 min. afforded after solvent removal 14.3 g of {1-[(4-methylphenyl)sulfonyl]-1H-imidazol-4-yl}acetonitrile (**20-1**) as white small crystals (98%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.94 (s, 1H), 7.80 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.28 (s, 1H), 3.62 (s, 2H), 2.42 (s, 3H); Mass Spectrum (Electrospray, M+H) = 262.

Di(tert-butyl)-5-(2-cyano-2-{1-[(4-methylphenyl)sulfonyl]-1H-imidazol-4-yl}ethyl)pyridin-2-ylimidodicarbonate (**20-2**)

To a THF solution containing {1-[(4-methylphenyl)sulfonyl]-1H-imidazol-4-yl}acetonitrile (**20-1**) and di(*tert*-butyl) 5-(bromomethyl)pyridin-2-ylimidodicarbonate at room temperature was added NaHMDS dropwise over 10 min. After 2 h the mixture was quenched with dilute NH_4Cl (50mL) and extracted with EtOAc (2 x 100 mL). The organic layers were washed with brine and dried over Na_2SO_4 to afford after solvent removal 3.2 g of crude product. Purification using automated flash chromatography gave 538 mg of a mixture containing mostly di(tert-butyl)-5-(2-cyano-2-{1-[(4-methylphenyl)sulfonyl]-1H-imidazol-4-yl}ethyl)pyridin-2-ylimidodicarbonate (**20-2**) along with starting ester and the by-product resulting from dialkylation: Mass Spectrum (Electrospray, M+H) = 568.

Tert-butyl 5-[2-cyano-2-(1H-imidazol-4-yl)ethyl]pyridin-2-ylcarbamate (**20-3**).

To a suspension of di(tert-butyl)-5-(2-cyano-2-{1-[(4-methylphenyl)sulfonyl]-1H-imidazol-4-yl}ethyl)pyridin-2-ylimidodicarbonate (**20-2**) (500mg, 0.88 mmol) in 1:1 THF:MeOH (8.0 mL) was added NaOMe (0.5 M MeOH solution, 0.08 mL, 0.04 mmol). The reaction was allowed to stir overnight at room temperature. At this time piperidine (0.09 mL, 0.88 mmol) was added and the mixture concentrated to dryness. The crude material was purified by automated flash gradient chromatorgraphy (0 to 5% MeOH/CH_2Cl_2 with 10% NH_3 in MeOH over 15 min.) to give 200 mg of tert-butyl 5-[2-cyano-2-(1H-imidazol-4-yl)ethyl]pyridin-2-ylcarbamate (**20-3**) along with traces of inseparable unalkylated and dialkylated impurities from previous step: Mass Spectrum (Electrospray, M+H) = 314.

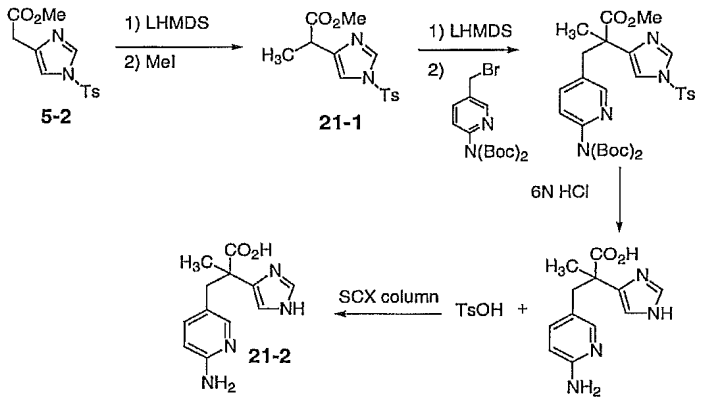
3-(6-Aminopyridin-3-yl)-2-[1-(4-methylphenyl)-1H-imidazol-4-yl]propanoic acid (**20-4**).

To an oven-dried flask charged with tert-butyl 5-[2-cyano-2-(1H-imidazol-4-yl)ethyl]pyridin-2-ylcarbamate (**20-3**) (120mg, 0.29 mmol), 4-methylphenyl boronic acid (62 mg, 0.58 mmol), and $[CuTMEDA(OH)]_2Cl_2$ (14 mg, 0.030 mmol) was added CH_2Cl_2 (1.2 mL). The mixture was evacuated and then pressurized with a ballon containing dry O_2 (1 atm). The reaction was allowed to stir vigorously overnight at room temperature and then filtered over Celite. The filtrate was concentrated to give 170 mg of crude material which was purified by automated flash chromatography (50 to 100% EtOAc/hexanes over 20min.) to give 60 mg of a mixture containing mono-Boc and bis-Boc protected N-arylated products. The

mixture also contained both N-aryl regioisomers (1,4 and 1,5 disubstituted) in approx. 1:1 ratio as evident by HPLC and LC-MS.

In a scintillation vial containing the above mixture (60mg) was added 1 mL 6N HCl. The vial was placed in a 95 °C oil bath and stirred overnight. At this time the crude was concentrated to near dryness, washed with acetonitrile and concentrated once again. This process was repeated twice more to give a foam. Purification by reverse-phase HPLC afforded 19 mg of 3-(6-aminopyridin-3-yl)-2-[1-(4-methylphenyl)-1H-imidazol-4-yl]propanoic acid (**20-4**) as a bis TFA salt: ^{1}H NMR (D_2O, 400 MHz) δ 8.94 (s, 1H), 7.63 (m, 2H), 7.49 (s, 1H), 7.28 (m, 4H), 6.80 (d, 1H, J = 9.2 Hz), 4.10 (X of ABX, app t, 1H, J = 7.7 Hz), 3.19 (A of ABX, 1H, J = 14.1, 7.7 Hz), 3.01 (B of ABX, 1H, J = 14.1, 7.7), 2.24 (s, 3H); Mass Spectrum (Electrospray, M+H) = 323.

Scheme 21



Methyl 2-{1-[(4-methylphenyl)sulfonyl]-1H-imidazol-4-yl}propanoate (**21-1**).

To a THF solution (10 mL) at –78 °C containing methyl {1-[(4-methylphenyl)sulfonyl]-1*H*-imidazol-4-yl}acetate (**5-2**) (1.00 g, 3.40 mmol) was added LiHMDS (1.0 M THF, 3.2 mL, 3.2 mmol) dropwise. After stirring at this temperature for 30 min. the enolate solution was cannula transferred to a 0 °C pre-cooled THF/MeI solution (1 mL THF, 1.04 mL MeI, 17 mmol). Upon complete addition of the enolate solution the ice-bath was removed and the mixture allowed to warm to room temperature. After 3.5 h the mixture was quenched with sat. aq. NH_4Cl, diluted with 10 mL of H_2O and then repeatedly extracted with EtOAc (3x50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and

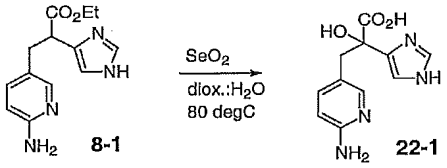
concentrated to dryness. Purification using flash chromatography over silica gave 350 mg of methyl 2-{1-[(4-methylphenyl)sulfonyl]-1H-imidazol-4-yl}propanoate (**21-1**) as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.94 (s, 1H), 7.82 (d, 2H, J = 8.4 Hz), 7.36 (d, 2H, J = 8.0 Hz), 7.27 (s, 1H), 7.18 (s, 1H), 3.74 (q, 1H, J = 6.8 Hz), 3.70 (s, 3H), 2.45 (s, 3H), 1.48 (d, 3H, J = 7.2 Hz); Mass Spectrum (Electrospray, M+H) = 309.

3-{6-[bis(tert-butoxycarbonyl)amino]pyridin-3-yl}-2-methyl-2-{1-[(4-methylphenyl)sulfonyl]-1H-imidazol-4-yl}propanoic acid (**21-2**).

To a THF solution (4.0 mL) of methyl 2-{1-[(4-methylphenyl)sulfonyl]-1H-imidazol-4-yl}propanoate (**21-1**) (100 mg, 0.32 mmol) at –78 °C was added LiHMDS (0.060 mL, 0.36 mmol, 1.0 THF solution) dropwise. After 15 min. at this temperature was added a THF solution of di(*tert*-butyl) 5-(bromomethyl)pyridin-2-ylimidodicarbonate in one portion. The mixture was allowed to warm to room temperature. Electrospray mass spectrum indicated product and product with loss of one *tert*-butoxycarbonyl group. To the solution was added aq. NH_4Cl (1 mL) and water (1 mL). The mixture was extracted repeatedly with EtOAc (3x20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated to dryness to give 196 mg of crude methyl 3-{6-[bis(tert-butoxycarbonyl)amino]pyridin-3-yl}-2-methyl-2-{1-[(4-methylphenyl)sulfonyl]-1H-imidazol-4-yl}propanoate.

In a 5 mL flask fitted with a condenser containing methyl 3-{6-[bis(tert-butoxycarbonyl)amino]pyridin-3-yl}-2-methyl-2-{1-[(4-methylphenyl)sulfonyl]-1H-imidazol-4-yl}propanoate was added 2.0 mL of 6N HCl. The mixture was placed in a 100 °C oil bath. After 1h the mixture was concentrated to dryness and purified by reverse-phase chromatography to afford 3-(6-aminopyridin-3-yl)-2-(1H-imidazol-4-yl)-2-methylpropanoic acid and tosic acid. The crude product was purified further by ion-exchange chromatography using an SCX column to afford 35 mg of 3-(6-aminopyridin-3-yl)-2-(1H-imidazol-4-yl)-2-methylpropanoic acid (**21-2**): ^{1}H NMR (D_2O, 400 MHz) δ 8.02 (s, 1H), 7.30 (s, 1H), 7.07 (d, J = 7.2 Hz, 1H), 6.82 (s, 1H), 6.51 (d, J = 8.4 Hz, 1H), 2.99 (A of AB, J = 14.0 Hz, 1H), 2.88 (B of AB, J = 14.0 Hz, 1H), 1.26 (s, 3H); Mass Spectrum (Electrospray, M+H) = 247.

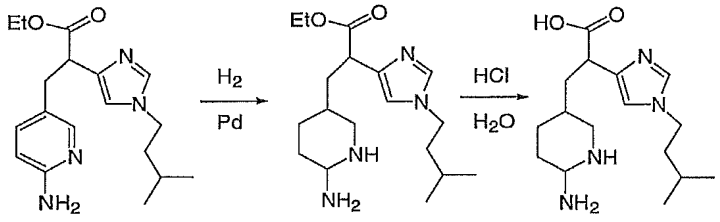
Scheme 22



3-(6-Aminopyridin-3-yl)-2-hydroxy-2-(1H-imidazol-4-yl)propanoic acid (**22-1**).

In a 20 mL scintillation vial containing an aqueous dioxane solution (5.0 mL dioxane, 1.0 mL water) of ethyl 3-(6-aminopyridin-3-yl)-2-(1H-imidazol-4-yl)propanoate (**8-1**) (50 mg, 0.19 mmol) was added selenium dioxide (SeO_2, 213 mg, 1.9 mmol). The vial was sealed and placed in an 80 °C oil bath and stirred overnight. The crude was passed over a short Celite plug, rinsed with 3-5 mL H_2O. The resulting filtrate was concentrated to dryness and purified by reverse-phase chromatography to give 22mg of a yellow foam. The crude foam was further purified by ion-exchange chromatography by applying sample onto an SCX column using 1:1 CH_3CN:H_2O (pH 4-5) and then eluting with methanolic ammonia to give 11 mg of 3-(6-aminopyridin-3-yl)-2-hydroxy-2-(1H-imidazol-4-yl)propanoic acid (**22-1**) as free base: ^{1}H NMR (D_2O, 400 MHz) δ 7.78 (s, 1H), 7.51 (s, 1H), 7.45 (d, J = 8.8 Hz, 1H), 7.02 (s, 1H), 6.60 (d, J = 8.8 Hz, 1H), 3.15 (A of AB, J = 14.0 Hz, 1H), 3.0 (B of AB, J = 14.0 Hz, 1H); Mass Spectrum (Electrospray, M+H) = 249.

Scheme 23



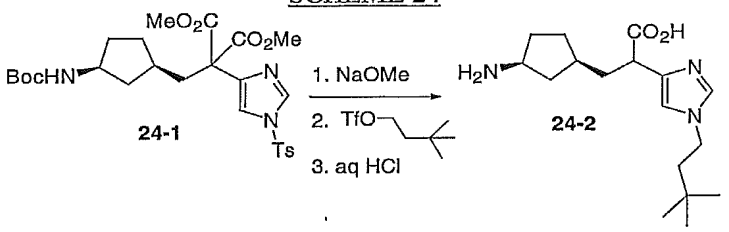
23-1 23-2 23-3

3-(6-amino-2,3,4,5-tetrahydropyridin-3-yl)-2-(1-isopentyl-1H-imidazol-4-yl)propanoic acid (**23-3**)

To a solution of 50 mg (0.15 mmol) ethyl 3-(6-aminopyridin-3-yl)-2-(1-isopentyl-1H-imidazol-4-yl)propanoate (**23-1**, prepared as described for **8-3**) in 10 mL EtOH was added 0.15 mL (0.15 mmol) 1 M HCl and the resulting solution was purged with argon after which 50 mg $Pd(OH)_2$ was added. The reaction mixture was hydrogenated under 1 atm H_2, stirring at 65 °C, for 18 h. The reaction mixture was allowed to cool to room temperature, filtered on celite, rinsed with EtOH, and concentrated in vacuo to give 54 mg ethyl 3-(6-amino-2,3,4,5-tetrahydropyridin-3-yl)-2-(1-isopentyl-1H-imidazol-4-yl)propanoate (**23-2**, diastereomeric mixture) as a thick gel. Electrospray Mass Spectrum M+H=335.

A solution of 54 mg (0.15 mmol) ethyl 3-(6-amino-2,3,4,5-tetrahydropyridin-3-yl)-2-(1-isopentyl-1H-imidazol-4-yl)propanoate (**23-2**) in 10 mL 6N HCl was heated to 65 °C for 75 minutes. The reaction mixture was concentrated in vacuo, water was added and the reaction mixture was concentrated in vacuo (process repeated twice) to give 66 mg 3-(6-amino-2,3,4,5-tetrahydropyridin-3-yl)-2-(1-isopentyl-1H-imidazol-4-yl)propanoic acid dihydrochloride (**23-3**, diastereomeric mixture). ^{1}H NMR (400 MHz, D_2O) δ 8.60 (s, 1H); 7.40 (s, 1H); 4.09 (t, 2H, *J*= 7.58 Hz); 3.98-3.88 (m, 1H); 3.37-3.27 (m, 1H); 2.96-2.86 (m, 1H); 2.61-2.34 (m, 2H); 2.06-1.93 (m, 1H); 1.87-1.72 (m, 2H); 1.70-1.56 (m, 3H); 1.45-1.31 (m, 2H); 0.76 (d, 6H, *J*= 6.62 Hz). Electrospray Mass Spectrum M+H=307.

SCHEME 24



3-[(1S,3S)-3-aminocyclopentyl]-2-[1-(3,3-dimethylbutyl)-1H-imidazol-4-yl]propanoic acid (**24-2**)

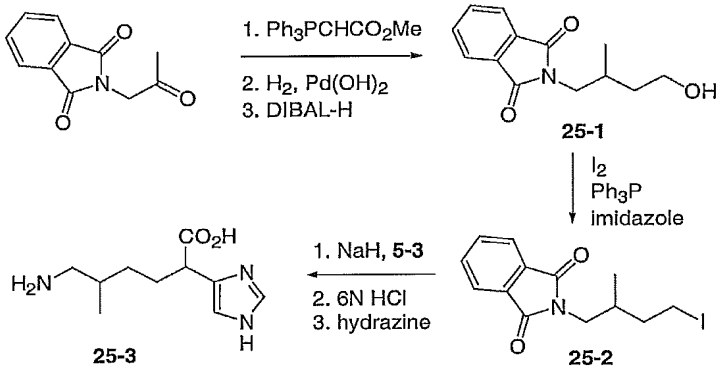
To a solution of dimethyl 2-({(1S,3S)-3-[(tert-butoxycarbonyl)amino]cyclopentyl}methyl)-2-{1-[(4-methylphenyl)sulfonyl]-1H-imidazol-4-yl}malonate (**24-1**, 250 mg, 0.46 mmol, obtained from the alkylation of **5-3** with tert-butyl-(1R,3S)-3-iodomethyl-cyclopentyl carbamate as described in the preparation of **4-3**) in THF/MeOH (1:1, 3 mL) was added 30% NaOMe in MeOH (0.004 mL, 0.02 mmol) and the reaction mixture was stirred at room temperature for 1 h. Piperidine (0.23 mL, 2.27 mmol) was added and the reaction mixture was stirred for 10 min. The reaction mixture was concentrated in vacuo and purified by flash chromatography (silica gel, 4% MeOH containing 10% NH_4OH in CH_2Cl_2 to 17%) to give 167 mg dimethyl 2-({(1S,3S)-3-[(tert-butoxycarbonyl)amino]cyclopentyl}methyl)-2-(1H-imidazol-4-yl)malonate.

To a solution of dimethyl 2-({(1S,3S)-3-[(tert-butoxycarbonyl)amino]cyclopentyl}methyl)-2-(1H-imidazol-4-yl)malonate (157 mg, 0.4 mmol) in CH_2Cl_2 (3 mL) was added diisopropylethylamine (0.08 mL, 0.44 mmol) and 3,3-dimethylbutyl trifluoromethanesulfonate (84 mg, 0.36 mmol, obtained from 3,3-dimethylbutanol and triflic anhydride) and the reaction was stirred at room temperature. Addtiional amounts of diisopropylethylamine and 3,3-dimethylbutyl trifluoromethanesulfonate were added until reaction completion. The reaction mixture was diluted with CH_2Cl_2, washed with aqueous bicarbonate and brine, dried over sodium sulfate, concentrated in vacuo and purified by flash chromatography (silica gel, 0% MeOH containing 10% NH_4OH in CH_2Cl_2 to 12%) then (silica gel, 60% EtOAc in hexane to 100%) to give 109 mg of dimethyl 2-({(1S,3S)3-[(tert-

butoxycarbonyl)amino]cyclopentyl}methyl)-2-[1-(3,3-dimethylbutyl)-1H-imidazol-4-yl]malonate.

A solution of 2-({(1S,3S)3-[(tert-butoxycarbonyl)amino]cyclopentyl}methyl)-2-[1-(3,3-dimethylbutyl)-1H-imidazol-4-yl]malonate (100 mg, 0.21 mmol) in 6N HCl (5 mL) was heated at 100 °C for 1.75 h, concentrated in vacuo, azeotroped from water and acetonitrile to give 88 mg 3-[(1S,3S)-3-aminocyclopentyl]-2-[1-(3,3-dimethylbutyl)-1H-imidazol-4-yl]propanoic acid dihydrochloride (**24-2**). ^{1}H NMR (400 MHz, D_2O) δ 8.57 (s, 1H); 7.35 (s, 1H); 4.07 (t, 2H, *J*= 8.4 Hz); 3.82-3.74 (m, 1H); 3.62-3.52 (m, 1H); 2.10-1.50 (m, 11H); 1.48-1.36 (m, 1H); 1.24-1.14 (m, 1H); 0.80 (s, 9H).

SCHEME 25



2-(4-hydroxy-2-methylbutyl)-1H-isoindole-1,3(2H)-dione (**25-1**)

To a solution of N-acetonylphthalimide (1g, 4.92 mmol) in DCE (10 mL) was methyl (triphenylphosphoranylidene)-acetate (1.97 g, 5.91 mmol) and the reaction mixture was stirred at 110 °C in a sealed tube for 1h25 and at 150 °C for 2h30. Methyl (triphenylphosphoranylidene)-acetate (1 g) was added and the reaction mixture was stirred at 110 °C for 18h, allowed to cool to room temperature, concentrated in vacuo and purified by flash chromatography (silica gel, 0% EtOAc in hexane to 40%) to give 985 mg of methyl (2E)-4-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-3-methylbut-2-enoate which was hydrogenated at 60 psi in MeOH, in the presence of catalytic $Pd(OH)_2$ to give after purification by flash chromatography (silica gel, 10% EtOAc in hexane to 60%) 731 mg of methyl 4-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-3-methylbutanoate.

To a solution of methyl 4-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-3-methylbutanoate (960 mg, 3.67 mmol) in THF (15 mL) cooled to –78 °C was added dropwise diisobutyl aluminium (5.5 mL, 5.5 mmol, 1M in THF) and the reaction was stirred at –78 °C for 2h. Diisobutyl aluminium (1.5 eq) was added, the reaction was allowed to slowly warm to room temperature over a period of 18h. The reaction mixture was quenched with aqueous sodium potassium tartrate, extracted with EtOAc, dried over sodium sulfate, concentrated in vacuo and purified by flash chromatography (silica gel, 50% EtOAc in hexane to 100%) to give 367 mg 2-(4-hydroxy-2-methylbutyl)-1H-isoindole-1,3(2H)-dione (**25-1**, 90% pure, carried as is in the next step). ES MS M+1= 234.28

2-(4-iodo-2-methylbutyl)-1H-isoindole-1,3(2H)-dione (**25-2**)

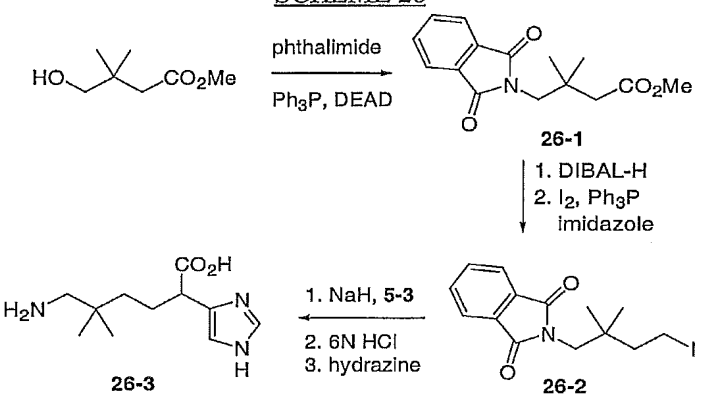
To a solution of 2-(4-hydroxy-2-methylbutyl)-1H-isoindole-1,3(2H)-dione (**25-1**, 367 mg, 1.57 mmol) in CH_2Cl_2 (10 mL) was added imidazole (134 mg, 1.97 mmol), triphenylphosphine (413 mg, 1.57 mmol) and iodine (480 mg, 1.89 mmol) and was stirred at room temperature for 2h.. The reaction mixture was concentrated in vacuo and purified by flash chromatography (silica gel, 0% EtOAc in hexane to 30%) to give 338 mg 2-(4-iodo-2-methylbutyl)-1H-isoindole-1,3(2H)-dione (**25-2**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90-7.80 (m, 2H); 7.78-7.68 (m, 2H); 3.65-3.51 (m, 2H); 3.37-3.28 (m, 1H); 3.21-3.11 (m, 1H); 2.20-2.06 (m, 1H); 2.01-1.88 (m, 1H);1.77-1.65 (m, 1H);0.95 (d, 3H, *J*= 7.0 Hz).

6-amino-2-(1H-imidazol-4-yl)-5-methylhexanoic acid (**25-3**)

6-amino-2-(1H-imidazol-4-yl)-5-methylhexanoic acid (**25-3**) was prepared from alkylation of **5-3** with 2-(4-iodo-2-methylbutyl)-1H-isoindole-1,3(2H)-dione (**25-2**) using a similar procedure as described for the preparation of **5-4** from **5-3** (Scheme 5), followed by ester hydrolysis/phthalimide removal with 6N HCl/hydrazine using a similar procedure as described for the preparation of **7-6** from **7-5** (Scheme 7).

6-amino-2-(1H-imidazol-4-yl)-5-methylhexanoic acid dihydrochloride, 1:1 mixture of diastereoisomers. ^{1}H NMR (400 MHz, D_2O) δ 8.55 (s, 1H); 7.29 (s, 1H); 3.82 (t, 2H, *J*= 7.9Hz); 2.88-2.78 (m, 1H); 2.68-2.58 (m, 1H); 2.10-1.64 (m, 3H); 1.36-0.96 (m, 2H); 0.85 (d, 1.5H, *J*= 6.7Hz); 0.83 (d, 1.5H, *J*= 6.7Hz).

SCHEME 26



methyl 4-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-3,3-dimethylbutanoate (**26-1**)

To a solution of methyl 4-hydroxy-3,3-dimethylbutanoate (3.45 g, 23.6 mmol, obtained from 2,2-dimethyl succinic anhydride according to US 5,428,033) in THF (50 mL) cooled to 0 °C was added phthalimide (4.17 g, 28.3 mmol), triphenylphosphine (7.43 g, 28.3 mmol) and diethylazodicarboxylate dropwise (4.09 mL, 26 mmol) and the reaction mixture was stirred, allowed to warm to room temperature over 18 h. The reaction mixture was concentrated in vacuo and purified by flash chromatography (silica gel, 20% EtOAc in hexane to 60%) to give 1.56 g methyl 4-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-3,3-dimethylbutanoate (**26-1**, 65% pure, carried as is in the next step). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90-7.80 (m, 2H); 7.78-7.68 (m, 2H); 3.67 (s, 5H); 2.33 (s, 2H); 1.10 (s, 6H).

2-(4-iodo-2,2-dimethylbutyl)-1H-isoindole-1,3(2H)-dione (**26-2**)

Prepared from methyl 4-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-3,3-dimethylbutanoate **26-1** by reduction and iodination using a similar procedure as described for the preparation of 2-(4-iodo-2-methylbutyl)-1H-isoindole-1,3(2H)-dione (**25-2**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90-7.83 (m, 2H); 7.78-7.70 (m, 2H); 3.51 (s, 2H); 3.37-3.27 (m, 1H); 2.02-1.92 (m, 1H); 0.97 (s, 6H).

6-amino-2-(1H-imidazol-4-yl)-5,5-dimethylhexanoic acid (**26-3**)

Prepared from 2-(4-iodo-2,2-dimethylbutyl)-1H-isoindole-1,3(2H)-dione (**26-2**) and **5-3** using as similar procedure (alkylation, hydrolysis and phthalimide removal) as described for the preparation of 6-amino-2-(1H-imidazol-4-yl)-5-methylhexanoic acid (**25-3**). HRMS ES calculated for $C_{11}H_{19}N_3O_2$: 226.1550, found: 226.1561.

Typical tablet cores suitable for administration of carboxypeptidase U inhibitors are comprised of, but not limited to, the following amounts of standard ingredients:

Excipient	General Range (%)	Preferred Range (%)	Most Preferred Range (%)
mannitol	10-90	25-75	30-60
microcrystalline cellulose	10-90	25-75	30-60
magnesium stearate	0.1-5.0	0.1-2.5	0.5-1.5

Mannitol, microcrystalline cellulose and magnesium stearate may be substituted with alternative pharmaceutically acceptable excipients.

Composition Example 1

Tablet Preparation

Tablets containing 25.0, 50.0, and 100.0 mg., respectively, of the following active compounds are prepared as illustrated below (compositions A-C). Active I is compound 3-(6-amino-5-methylpyridin-3-yl)-2-(1H-imidazol-4-yl)propanoic acid.

	Amount-(mg)		
Component	A	B	C
Active I	25	50	100
Microcrystalline cellulose	37.25	100	200
Modified food corn starch	37.25	4.25	8.5
Magnesium stearate	0.5	0.75	1.5

All of the active compound, cellulose, and a portion of the corn starch are mixed and granulated to 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium

stearate. The resulting granulation is then compressed into tablets containing 25.0, 50.0, and 100.0 mg, respectively, of active ingredient per tablet.

Composition Example 2

Tablet Preparation

Exemplary compositions of compound 3-(6-amino-5-methylpyridin-3-yl)-2-(1H-imidazol-4-yl)propanoic acid (Active I) tablets are shown below:

Component	0.25 mg	2 mg	10 mg	50 mg
Active I	0.500%	1.000%	5.000%	14.29%
mannitol	49.50%	49.25%	47.25%	42.61%
microcrystalline cellulose	49.50%	49.25%	47.25%	42.61%
magnesium stearate	0.500%	0.500%	0.500%	0.500%

2, 10 and 50 mg tablets were film-coated with an aqueous dispersion of hydroxypropyl cellulose, hydroxypropyl methylcellulose and titanium dioxide, providing a nominal weight gain of 2.4%.

Tablet preparation via direct compression

Active I, mannitol and microcrystalline cellulose were sieved through mesh screens of specified size (generally 250 to 750 μm) and combined in a suitable blender. The mixture was subsequently blended (typically 15 to 30 min) until the drug was uniformly distributed in the resulting dry powder blend. Magnesium stearate was screened and added to the blender, after which a precompression tablet blend was achieved upon additional mixing (typically 2 to 10 min). The precompression tablet blend was then compacted under an applied force, typically ranging from 0.5 to 2.5 metric tons, sufficient to yield tablets of suitable physical strength with acceptable disintegration times (specifications will vary with the size and potency of the compressed tablet). In the case of the 2, 10 and 50 mg potencies, the tablets were dedusted and film-coated with an aqueous dispersion of water-soluble polymers and pigment.

Tablet preparation via dry granulation

Alternatively, a dry powder blend is compacted under modest forces and remilled to afford granules of specified particle size. The granules are then mixed with magnesium stearate and tabletted as stated above.

Composition Example 3

Intravenous Formulations

Intravenous formulations of compound 3-(6-amino-5-methylpyridin-3-yl)-2-(1H-imidazol-4-yl)propanoic acid (Active I) were prepared according to general intravenous formulation procedures.

Component	Estimated range
Active I	0.12 - 0.61 mg
D-glucuronic acid	0.5 - 5 mg
Mannitol NF	50-53 mg
1 N Sodium Hydroxide	q.s. pH 3.9 - 4.1
Water for injection	q.s. 1.0 mL

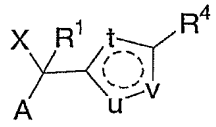
Exemplary compositions A-C are as follows:

Component	A	B	C
Active I	0.50 mg	0.25 mg	0.12 mg
D-glucuronic acid	1.94 mg	1.94 mg	1.94 mg
Mannitol NF	51.2 mg	51.2 mg	51.2 mg
1 N Sodium Hydroxide	q.s. pH 4.0	q.s. pH 4.0	q.s. pH 4.0
Water for injection	q.s. 1.0 mL	q.s. 1.0 mL	q.s. 1.0 mL

Various other buffer acids, such as L-lactic acid, acetic acid, citric acid or any pharmaceutically acceptable acid/conjugate base with reasonable buffering capacity in the pH range acceptable for intravenous administration may be substituted for glucuronic acid.

WHAT IS CLAIMED IS:

1. A compound of the general formula:



and pharmaceutically acceptable salts thereof, wherein

t is N or N($R^{2"}$), u is C(R^3) or N($R^{2'}$), and v is C(R^2), N or N(R^2),

provided that,

1) when t is N and u is C(R^3), then v is N(R^2),

2) when t is N and u is N($R^{2'}$), then v is C(R^2), and

3) when t is N($R^{2"}$) and u is C(R^3), then v is N or N(R^2);

A is

a) $COOR^5$,

b) tetrazole, or

c) a carboxylic acid isostere,

wherein R^5 is

1) hydrogen,

2) unsubstituted C_{1-8} alkyl, or

3) substituted C_{1-8} alkyl, wherein the alkyl substituent is selected from the group consisting of

i) aryl,

ii) heterocycle,

iii) $-NR^6R^7$,

iv) $-OR^6$, and

v) $-CHR^6OC(O)R^7$,

wherein R^6 and R^7 are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, and aryl;

X is

a) C_{1-6} alkyl, substituted with one or more basic groups, or

b) Y-W,

wherein Y is

1) (CR^8R^9),

2) $(CR^8R^9)(CR^{10}R^{11})$,

3) $(CR^8R^9)(CR^{10}R^{11})(CR^{12}R^{13})$, or

4) a bond,

wherein R^8, R^{10}, and R^{12}, are independently selected from the group consisting of hydrogen, C 1-4 alkyl, OR^{14}, F, and $NR^{14}R^{15}$,

wherein R^{14} and R^{15} are independently selected from the group consisting of hydrogen and C_{1-4} alkyl, and

wherein R^9, R^{11}, and R^{13} are independently selected from the group consisting of hydrogen, F and C_{1-4} alkyl,

and wherein W is

1) a C_{3-7} cycloalkyl ring wherein at least one ring carbon atom is substituted with a basic group,

2) a 4- to 7-membered saturated or unsaturated heterocyclic ring, having 1-4 nitrogen ring atoms, wherein each ring carbon atom is independently unsubstituted or mono- or bi-substituted with a basic group, halogen, or C_{1-4} alkyl, or

3) a 6- or 10- membered aryl ring system, wherein at least one ring carbon atom is substituted with a basic group;

R^1 is selected from the group consisting of

a) hydrogen,

b) C_{1-4} alkyl,

c) OR^{16},

d) F, and

e) $NR^{16}R^{17}$,

wherein R^{16} and R^{17} are independently selected from the group consisting of hydrogen and C 1-4 alkyl;

R^2 is selected from the group consisting of

a) hydrogen,

b) methyl,

c) phenyl, unsubstituted or independently mono- or di-substituted with a substitutent selected from the group consisting of halogen, phenyl, C_{1-4} alkyl, CF_3, CN, OCH_3, NH_2, NO_2, pyridine and pyrimidine,

d) C_{1-4} alkenyl, and

e) A^1-$(A^2)_{0-1}$-$(A^3)_{0-1}$-$(A^4)_{0-1}$-A^5, wherein

A^1 is C_{1-7} alkylene, wherein each carbon atom is independently unsubstituted or mono- or di-substituted with a substitutent selected from the group consisting of F, CF_3 and C_{1-4} alkyl,

A^2 is selected from the group consisting of C(O), C(O)NH, NHC(O), and -$NHSO_2$,

A^3 is a bond or C_{1-3} alkylene, where each carbon atom is independently unsubstituted or mono- or di-substituted with C_{1-4} alkyl,

A^4 is a bond, O, or OCH_2, and

A^5 is

1) phenyl, unsubstituted or independently mono- or di-substituted with a substitutent selected from the group consisting of halogen, phenyl, C_{1-4} alkyl, CF_3, CN, OCH_3 and NH_2,

2) pyridinyl,

3) naphthyl,

4) CF_3

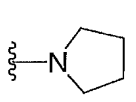
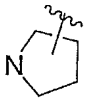
5) C_{1-5} alkyl,

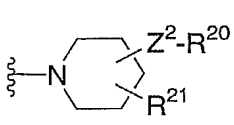
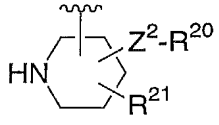
6) -$NR^{18}R^{19}$, wherein R^{18} and R^{19} are independently selected from the group of consisting of hydrogen and C_{1-4} alkyl,

7) OH,

8) COOH,

9) C_{3-10} carbocyclic ring system, unsubstituted or independently mono- or di-substituted with a substituent selected from the group consisting of NH_2 and C_{1-4} alkyl,

10)  or  , or

11)  or 

wherein Z^2 is a bond or C_{1-4} alkylene, R^{20} and R^{21} are independently selected from the group consisting of hydrogen, phenyl, CN or difluorophenyl;

$R^{2'}$ is selected from the group consisting of

a) hydrogen,

b) methyl,

c) phenyl, unsubstituted or independently mono- or di-substituted with a substitutent selected from the group consisting of halogen, phenyl, C_{1-4} alkyl, CF_3, CN, OCH_3, NH_2, NO_2, pyridine and pyrimidine,

d) C_{1-4} alkenyl, and

e) $A^{1'}$-$(A^{2'})_{0-1}$-$(A^{3'})_{0-1}$-$(A^{4'})_{0-1}$-$A^{5'}$, wherein

$A^{1'}$ is C_{1-7} alkylene, wherein each carbon atom is independently unsubstituted or mono- or di-substituted with a substitutent selected from the group consisting of F, CF_3 and C_{1-4} alkyl,

$A^{2'}$ is selected from the group consisting of C(O), C(O)NH, NHC(O), and -$NHSO_2$,

$A^{3'}$ is a bond or C_{1-3} alkylene, where each carbon atom is independently unsubstituted or mono- or di-substituted with C_{1-4} alkyl,

$A^{4'}$ is a bond, O, or OCH_2, and

$A^{5'}$ is

1) phenyl, unsubstituted or independently mono- or di-substituted with a substitutent selected from the group consisting of halogen, phenyl, C_{1-4} alkyl, CF_3, CN, OCH_3 and NH_2,

2) pyridinyl,

3) naphthyl,

4) CF_3

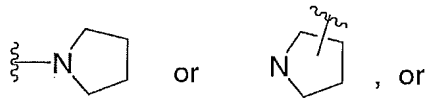
5) C_{1-5} alkyl,

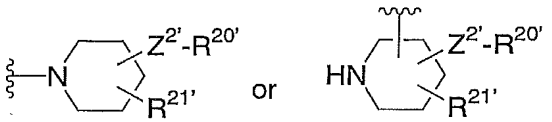
6) -$NR^{18'}R^{19'}$, wherein $R^{18'}$ and $R^{19'}$ are independently selected from the group of consisting of hydrogen and C_{1-4} alkyl,

7) OH,

8) COOH,

9) C_{3-10} carbocyclic ring system, unsubstituted or independently mono- or di-substituted with a substituent selected from the group consisting of NH_2 and C_{1-4} alkyl,

10)  or , or

11) 

wherein $Z^{2'}$ is a bond or C_{1-4} alkylene, $R^{20'}$ and $R^{21'}$ are independently selected from the group consisting of hydrogen, phenyl, CN or difluorophenyl;

$R^{2"}$ is selected from the group consisting of

a) hydrogen,

b) methyl,

c) phenyl, unsubstituted or independently mono- or di-substituted with a substitutent selected from the group consisting of halogen, phenyl, C_{1-4} alkyl, CF_3, CN, OCH_3, NH_2, NO_2, pyridine and pyrimidine,

d) C_{1-4} alkenyl, and

e) $A^{1"}$-$(A^{2"})_{0-1}$-$(A^{3"})_{0-1}$-$(A^{4"})_{0-1}$-$A^{5"}$, wherein

$A^{1"}$ is C_{1-7} alkylene, wherein each carbon atom is independently unsubstituted or mono- or di-substituted with a substitutent selected from the group consisting of F, CF_3 and C_{1-4} alkyl,

$A^{2"}$ is selected from the group consisting of C(O), C(O)NH, NHC(O), and -$NHSO_2$,

$A^{3"}$ is a bond or C_{1-3} alkylene, where each carbon atom is independently unsubstituted or mono- or di-substituted with C_{1-4} alkyl,

$A^{4"}$ is a bond, O, or OCH_2, and

$A^{5"}$ is

1) phenyl, unsubstituted or independently mono- or di-substituted with a substitutent selected from the group consisting of halogen, phenyl, C_{1-4} alkyl, CF_3, CN, OCH_3 and NH_2,

2) pyridinyl,

3) naphthyl,

4) CF_3

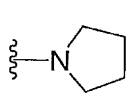
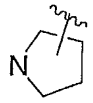
5) C_{1-5} alkyl,

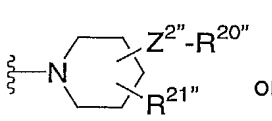
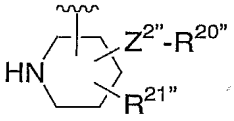
6) $-NR^{18"}R^{19"}$, wherein $R^{18"}$ and $R^{19"}$ are independently selected from the group of consisting of hydrogen and C_{1-4} alkyl,

7) OH,

8) COOH,

9) C_{3-10} carbocyclic ring system, unsubstituted or independently mono- or di-substituted with a substituent selected from the group consisting of NH_2 and C_{1-4} alkyl,

10)  or  , or

11)  or 

wherein $Z^{2"}$ is a bond or C_{1-4} alkylene, $R^{20"}$ and $R^{21"}$ are independently selected from the group consisting of hydrogen, phenyl, CN or difluorophenyl;

R^3 is

a) hydrogen,

b) unsubstituted or substituted C_{1-6} alkyl,

c) unsubstituted or substituted phenyl,

d) unsubstituted or substituted naphthyl, or

e) unsubstituted or substituted heterocycle,

wherein one or more substituents in substituted alkyl is independently selected from the group consisting of F, C_{1-6} alkyl, phenyl, naphthyl, and heterocyle, and one or more substituents in substituted phenyl, substituted naphthyl and

substituted heterocycle is independently selected from the group consisting of phenyl, naphthyl, heterocyle, -CF_3, -CN, C_{1-6} alkyl, hydroxy, C_{1-4} alkoxy; halogen, -NO_2, -$NR^{23}R^{24}$, -SO_2R^{23}, $SO_2NR^{23}R^{24}$, -$CONR^{23}R^{24}$, or COR^{23}, wherein R^{23} and R^{24} are independently selected hydrogen and C_{1-4} alkyl; and

R^4 is

a) hydrogen,

b) unsubstituted or substituted C_{1-6} alkyl,

c) unsubstituted or substituted phenyl,

d) unsubstituted or substituted naphthyl,

e) unsubstituted or substituted heterocycle, or

f) unsubstituted or substituted C_{1-4} alkylenearyl,

wherein one or more substituents in substituted alkyl is independently selected from the group consisting of F, C_{1-6} alkyl, phenyl, naphthyl, and heterocyle, and one or more substituents in substituted phenyl, substituted naphthyl and substituted heterocycle is independently selected from the group consisting of phenyl, naphthyl, heterocyle, -CF_3, -CN, C_{1-6} alkyl, hydroxy, C_{1-4} alkoxy; halogen, -NO_2, -$NR^{25}R^{26}$, -SO_2R^{25}, $SO_2NR^{25}R^{26}$, -$CONR^{25}R^{26}$, or COR^{25}, wherein R^{25} and R^{26} are independently selected hydrogen and C_{1-4} alkyl.

2. A compound of Claim 1, or pharmaceutically acceptable salt thereof, wherein A is COOH, R^1 is hydrogen, F or OH, R^3 is hydrogen, and R^4 is hydrogen.

3. A compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein $R^{2'}$ is hydrogen and

$R^{2"}$ is

a) phenyl, unsubstituted or substituted with C_{1-4} alkyl, or

b) $A^{1"}$-$A^{5"}$, wherein

$A^{1"}$ is C_{1-2} alkylene, wherein each carbon atom is independently unsubstituted or mono- or di-substituted with a substitutent selected from the group consisting of F, CF_3 and C_{1-4} alkyl , and

$A^{5"}$ is

1) phenyl, unsubstituted or independently mono- or di-substituted with a substitutent selected from the group consisting of halogen, phenyl, C_{1-4} alkyl, CF_3, CN, OCH_3 and NH_2, or

2) C_{1-5} alkyl.

4. A compound of Claim 2, or pharmaceutically acceptable salt thereof, wherein X is

X is

a) C_{1-4} alkyl, substituted with NH_2, or

b) Y-W,

wherein Y is $(CH_2)_{1-2}$

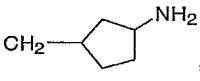
and wherein W is

1) a cyclopentyl substituted with NH_2,

2) a 4-7 membered saturated or unsaturated heterocyclic ring, having 1-4 nitrogen ring atoms, wherein each ring carbon atom is independently unsubstituted, mono- or bi-substituted with NH_2, CH_3 or Cl.

5. A compound of Claim 4, or pharmaceutically acceptable salt thereof, wherein X is selected from the group consisting of

$(CH_2)_3NH_2$, $(CH_2)_4NH_2$, $(CH_2)_2CH(CH_3)CH_2NH_2$,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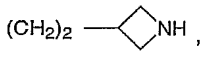
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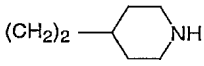
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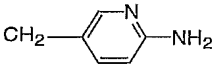
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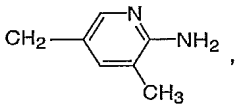
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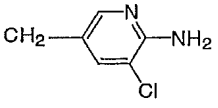
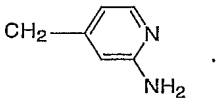

, and

.

6. A compound of Claim 5, or pharmaceutically acceptable salt thereof, wherein R^2 is selected from the group consisting of hydrogen,

methyl,

phenyl, unsubstituted or substituted with C_{1-4} alkyl, NH_2, CN, NO_2, pyridine or pyrimidine,

C_{1-4} alkenyl and

A^1-$(A^2)_{0-1}$-$(A^3)_{0-1}$-$(A^4)_{0-1}$-A^5, wherein

A^1 is $(CH_2)_{1-7}$ or $CH(CH_3)$,

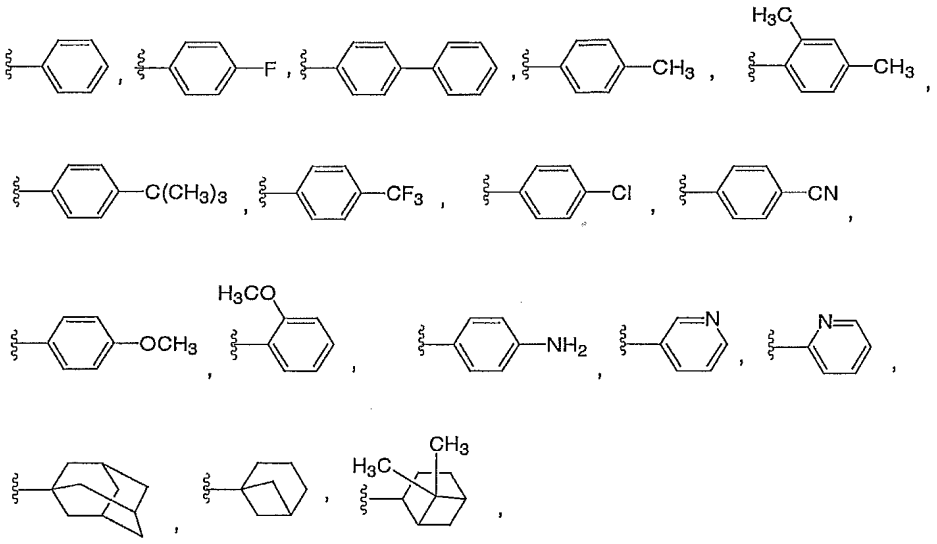
A^2 is selected from the group consisting of C(O), C(O)NH, NHC(O), and -$NHSO_2$,

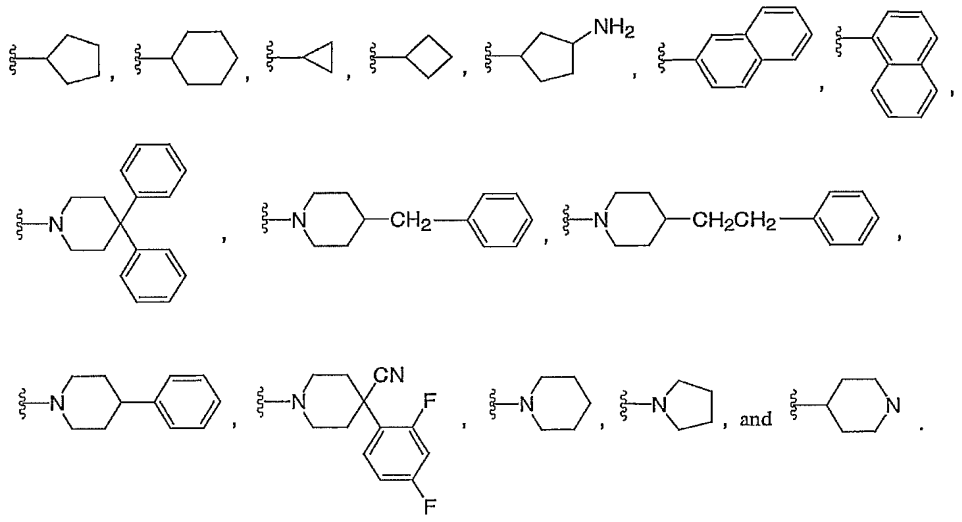
A^3 is a bond, $(CH_2)_{1-3}$ or $C(CH_3)_2CH_2$,

A^4 is a bond, O, or OCH_2, and

A^5 is selected from the group consisting of

CF_3, CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, $CH(CH_2CH_3)_2$, $N(CH_2CH_3)_2$, $N(CH_3)_2$, NH_2, OH, COOH,





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7. A compound of Claim 6, or pharmaceutically acceptable salt thereof, selected from the group consisting of

3-(6-aminopyridin-3-yl)-2-(1*H*-imidazol-4-yl) propanoic acid

3-(6-amino-5-methylpyridin-3-yl)-2-(1H-imidazol-4-yl)propanoic acid

3-(6-amino-4-methylpyridin-3-yl)-2-(1H-imidazol-4-yl)propanoic acid

3-(6-amino-2-methylpyridin-3-yl)-2-(1H-imidazol-4-yl)propanoic acid

3-(6-amino-5-chloropyridin-3-yl)-2-(1H-imidazol-4-yl)propanoic acid

3-(2-aminopyridin-4-yl)-2-(1H-imidazol-4-yl)propanoic acid

3-(6-aminopyridin-2-yl)-2-(1H-imidazol-4-yl)propanoic acid

3-[(1R,3S)-3-aminocyclopentyl]-2-(1H-imidazol-4-yl)propanoic acid

3-[(1S,3R)-3-aminocyclopentyl]-2-(1H-imidazol-4-yl)propanoic acid

3-[(1S,3S)-3-aminocyclopentyl]-2-(1H-imidazol-4-yl)propanoic acid

3-[(1R,3R)-3-aminocyclopentyl]-2-(1H-imidazol-4-yl)propanoic acid

3-(4-aminocyclohexyl)-2-(1H-imidazol-4-yl)propanoic acid

3-(3-aminocyclohexyl)-2-(1H-imidazol-4-yl)propanoic acid

2-(1H-imidazol-4-yl)-4-pyrrolidin-3-ylbutanoic acid

2-(1H-imidazol-4-yl)-4-piperidin-3-ylbutanoic acid

2-(1H-imidazol-4-yl)-5-(1H-imidazol-5-yl)pentanoic acid

2-(1H-imidazol-4-yl)-5-(1H-imidazol-5-yl)butanoic acid

4-azetidin-3-yl-2-{1-[(4-methylphenyl)sulfonyl]-1H-imidazol-4-yl}butanoic acid

6-amino-2-(1-isopentyl-1*H*-imidazol-4-yl)hexanoic acid

5-amino-2-(1*H*-imidazol-4-yl)pentanoic acid

7-amino-2-(1*H*-imidazol-4-yl)heptanoic acid

6-methylamino-2-(1*H*-imidazol-4-yl)hexanoic acid

6-dimethylamino-2-(1*H*-imidazol-4-yl)hexanoic acid

3-(6-aminopyridin-3-yl)-2-(1-butyl-1*H*-imidazol-4-yl)propanoic acid

3-(6-aminopyridin-3-yl)-2-(1-benzyl-1*H*-imidazol-4-yl)propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(cyclohexylmethyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(3-phenylpropyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(cyclopropylmethyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(2-piperidin-4-ylethyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(2-phenylethyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(2-ethylbutyl)-1*H*-imidazol-4-yl]propanoic acid

2-(1-allyl-1*H*-imidazol-4-yl)-3-(6-aminopyridin-3-yl)propanoic acid

3-(6-aminopyridin-3-yl)-2-(1-isobutyl-1*H*-imidazol-4-yl)propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(2-methoxyethyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(cyclobutylmethyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-(1-methyl-1*H*-imidazol-4-yl)propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(2,2-difluoro-2-pyridin-2-ylethyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(3-methylbenzyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(4-methylbenzyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(4-cyanobenzyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(3-methoxybenzyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-(1-isopropyl-1*H*-imidazol-4-yl)propanoic acid

3-(6-aminopyridin-3-yl)-2-{1-[3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)propyl]-1*H*-imidazol-4-yl}propanoic acid

3-(6-aminopyridin-3-yl)-2-{1-[4-(trifluoromethyl) benzyl]-1*H*-imidazol-4-yl}propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(2-chlorobenzyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(4-chlorobenzyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(carboxymethyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(2-methylbenzyl)-1*H*-imidazol-4-yl]propanoic acid

4-({4-[2-(6-aminopyridin-3-yl)-1-carboxyethyl]-1*H*-imidazol-1-yl}methyl)benzoic acid

3-(6-aminopyridin-3-yl)-2-[1-(3-chlorobenzyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-{1-[3-(benzyloxy) propyl]-1*H*-imidazol-4-yl}propanoic acid

4-{4-[2-(6-aminopyridin-3-yl)-1-carboxyethyl]-1*H*-imidazol-1-yl}butanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(pyridin-2-ylmethyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(3,3-dimethylbutyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(tetrahydrofuran-2-ylmethyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-{1-[2-(1*H*-pyrrol-1-yl)ethyl]-1*H*-imidazol-4-yl}propanoic acid

3-(6-aminopyridin-3-yl)-2-(1-ethyl-1*H*-imidazol-4-yl)propanoic acid

3-(6-aminopyridin-3-yl)-2-(1-propyl-1*H*-imidazol-4-yl)propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(tetrahydro-2*H*-pyran-2-ylmethyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(pyridin-3-ylmethyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(4,4,4-trifluorobutyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-(1-pentyl-1*H*-imidazol-4-yl)propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(4-nitrophenyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(4-cyanophenyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(2-cyanophenyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(2-nitrophenyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-(1-pyrimidin-2-yl-1*H*-imidazol-4-yl)propanoic acid

3-(6-aminopyridin-3-yl)-2-(1-hexyl-1*H*-imidazol-4-yl)propanoic acid

(2*R*)-3-(6-aminopyridin-3-yl)-2-[1-(2-cyclohexylethyl)-1*H*-imidazol-4-yl]propanoic acid

(2*R*)-2-{1-[2-(1-adamantyl)ethyl]-1*H*-imidazol-4-yl}-3-(6-aminopyridin-3-yl)propanoic acid

(2*R*)-3-(6-aminopyridin-3-yl)-2-[1-(2-cyclopropylethyl)-1*H*-imidazol-4-yl]propanoic acid

(2*R*)-3-(6-aminopyridin-3-yl)-2-{1-[2-(6,6-dimethylbicyclo[3.1.1]hept-2-yl)ethyl]-1*H*-imidazol-4-yl}propanoic acid

(2*R*)-3-(6-aminopyridin-3-yl)-2-(1-{2-[(1*S*,4*R*)-bicyclo[2.2.1]hept-2-yl]ethyl}-1*H*-imidazol-4-yl)propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(2-oxo-2-pyrrolidin-1-ylethyl)-1H-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-{1-[2-(benzylamino)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid

3-(6-aminopyridin-3-yl)-2-(1-{2-oxo-2-[(2-phenylethyl)amino]ethyl}-1*H*-imidazol-4-yl)propanoic acid

3-(6-aminopyridin-3-yl)-2-(1-{2-[(4-methoxyphenyl)amino]-2-oxoethyl}-1*H*-imidazol-4-yl)propanoic acid

3-(6-aminopyridin-3-yl)-2-{1-[2-(methylamino)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid

3-(6-aminopyridin-3-yl)-2-{1-[2-oxo-2-(4-phenylpiperidin-1-yl)ethyl]-1*H*-imidazol-4-yl}propanoic acid

3-(6-aminopyridin-3-yl)-2-{1-[2-(ethylamino)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid

3-(6-aminopyridin-3-yl)-2-{1-[2-(diethylamino)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(2-anilino-2-oxoethyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(2-oxo-2-piperidin-1-ylethyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-(1-{2-oxo-2-[(3-phenylpropyl)amino]ethyl}-1*H*-imidazol-4-yl)propanoic acid

3-(6-aminopyridin-3-yl)-2-{1-[2-(1,1'-biphenyl-4-ylamino)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid

3-(6-aminopyridin-3-yl)-2-{1-[2-(2-naphthylamino)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid

3-(6-aminopyridin-3-yl)-2-{1-[2-(cyclohexylamino)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid

3-(6-aminopyridin-3-yl)-2-{1-[2-(dimethylamino)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(1-methyl-2-oxo-2-pyrrolidin-1-ylethyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-Aminopyridin-3-yl)-2-[1-(3,3-dimethyl-2-oxobutyl)-1H-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(2-oxo-2-phenylethyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-{1-[2-(4-chlorophenyl)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid

3-(6-aminopyridin-3-yl)-2-{1-[2-(4-fluorophenyl)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid

3-(6-aminopyridin-3-yl)-2-{1-[2-(1,1'-biphenyl-4-yl)-2-oxoethyl]-1*H*-imidazol-4-

yl}propanoic acid

3-(6-aminopyridin-3-yl)-2-{1-[2-(4-cyanophenyl)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid

3-(6-aminopyridin-3-yl)-2-{1-[2-(4-methoxyphenyl)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid

3-(6-aminopyridin-3-yl)-2-{1-[2-(2-methoxyphenyl)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid

2-{1-[2-(1-adamantyl)-2-oxoethyl]-1*H*-imidazol-4-yl}-3-(6-aminopyridin-3-yl)propanoic acid

3-(6-aminopyridin-3-yl)-2-{1-[2-(4-methylphenyl)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid

2-{1-[2-(4-aminophenyl)-2-oxoethyl]-1*H*-imidazol-4-yl}-3-(6-aminopyridin-3-yl)propanoic acid

3-(6-aminopyridin-3-yl)-2-[1-(1-methyl-2-oxo-2-phenylethyl)-1*H*-imidazol-4-yl]propanoic acid

3-(6-aminopyridin-3-yl)-2-{1-[2-(2-naphthyl)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid

3-(6-aminopyridin-3-yl)-2-{1-[2-(2,4-dimethyl phenyl)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid

3-(6-aminopyridin-3-yl)-2-(1-{2-oxo-2-[4-(trifluoromethyl) phenyl]ethyl}-1*H*-imidazol-4-yl)propanoic acid

(2*R*)-3-(6-aminopyridin-3-yl)-2-{1-[2-(4,4-diphenylpiperidin-1-yl)-2-oxoethyl]-1H-imidazol-4-yl}propanoic acid

(2*R*)-3-(6-aminopyridin-3-yl)-2-{1-[2-(benzylamino)-2-oxoethyl]-1H-imidazol-4-yl}propanoic acid

(2*R*)-3-(6-aminopyridin-3-yl)-2-{1-[2-(4-benzylpiperidin-1-yl)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid

(2*R*)-3-(6-aminopyridin-3-yl)-2-(1-{2-[4-cyano-4-(2,4-difluorophenyl) piperidin-1-yl]-2-oxoethyl}-1*H*-imidazol-4-yl)propanoic acid

(2*R*)-3-(6-aminopyridin-3-yl)-2-(1-{2-oxo-2-[4-(2-phenylethyl)piperidin-1-yl]ethyl}-1*H*-imidazol-4-yl)propanoic acid

(2*R*)-3-(6-aminopyridin-3-yl)-2-{1-[2-(4-*tert*-butylphenyl)-2-oxoethyl]-1*H*-imidazol-4-yl}propanoic acid

3-(6-aminopyridin-3-yl)-2-(1-methyl-1H-imidazol-2-yl)propanoic acid

3-(6-aminopyridin-3-yl)-2-(1-benzyl-1H-imidazol-2-yl)propanoic acid

3-(6-aminopyridin-3-yl)-2-(5-butyl-1H-imidazol-2-yl)propanoic acid

3-(6-aminopyridin-3-yl)-2-(5-benzyl-1H-imidazol-2-yl)propanoic acid

5-[2-(1H-imidazol-4-yl)-2-(2H-tetraazol-5-yl)ethyl]pyridin-2-amine di-trifluoroacetate

(2*R*)-3-(6-aminopyridin-3-yl)-2-(1-isopentyl-1*H*-imidazol-4-yl)propanoic acid

3-(6-Aminopyridin-3-yl)-2-fluoro-2-(1H-imidazol-4-yl)propanoic acid

2-[1-(4-aminophenyl)-1H-imidazol-4-yl]-3-(6-aminopyridin-3-yl)propanoic acid

3-(6-Aminopyridin-3-yl)-2-(1-pyridin-2-yl-1H-imidazol-4-yl)propanoic acid

3-(6-Aminopyridin-3-yl)-2-[1-(4-methylphenyl)-1H-imidazol-4-yl]propanoic acid

3-{6-[bis(tert-butoxycarbonyl)amino]pyridin-3-yl}-2-methyl-2-{1-[(4-methylphenyl)sulfonyl]-1H-imidazol-4-yl}propanoic acid

3-(6-Aminopyridin-3-yl)-2-hydroxy-2-(1H-imidazol-4-yl)propanoic acid

2-(6-Aminopyridin-3-yl)-3-(1H-imidazol-5-yl)propanoic acid

3-(6-amino-2,3,4,5-tetrahydropyridin-3-yl)-2-(1-isopentyl-1H-imidazol-4-yl)propanoic acid

3-(6-aminopyridin-3-yl)-2-(1H-imidazol-4-ylmethyl)propanoic acid.

8. A composition comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.

9. A method for inhibiting carboxypeptidase U in a patient in need of such inhibition comprising administering to the patient a therapeutically effective amount of a compound of Claim 1.

10. A method for inhibiting thrombus formation in a patient in need of such inhibition comprising administering to the patient a therapeutically effective amount of a compound of Claim 1.

11. A method for inhibiting thrombus formation in a patient in need of such inhibition comprising administering to the patient a therapeutically effective amount of a compound of Claim 1 in combination with a therapeutically effective amount of an antiplatelet agent.

12. A method of Claim 11 wherein the antiplatelet agent is selected from the group consisting of a fibrinogen receptor antagonist, aspirin, a platelet

inhibitor, an ADP-induced platelet aggregation inhibitor, and a platelet aggregation inhibitor.

13. A method for inhibiting thrombus formation in a patient in need of such inhibition comprising administering to the patient a therapeutically effective amount of a compound of Claim 1 in combination with a therapeutically effective amount of an anticoagulant agent.

14. A method of Claim 13 wherein the anticoagulant agent is selected from the group consisting of warfarin, unfractionated heparin, low molecular weight heparin, a thrombin inhibitor, and a Factor Xa inhibitor.

15. A method for inhibiting thrombus formation in a patient in need of such inhibition comprising administering to the patient a therapeutically effective amount of a compound of Claim 1 in combination with a therapeutically effective amount of a thrombolytic agent.

16. A method for inhibiting thrombus formation in blood comprising adding to the blood a thrombus formation inhibiting amount of a compound of Claim 1.

17. The use of a compound of Claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inhibiting thrombus formation, treating thrombus formation, or preventing thrombus formation in a mammal.

18. A method for treating or preventing venous thromboembolism and pulmonary embolism in a patient in need of such treatment or prevention comprising administering to the patient a therapeutically or prophylactically effective amount of a compound of Claim 1.

19. A method for treating or preventing deep vein thrombosis in a patient in need of such treatment or prevention comprising administering to the patient a therapeutically or prophylactically effective amount of a compound of Claim 1.

20. A method for treating or preventing thromboembolic stroke in a patient in need of such treatment or prevention comprising administering to the patient a therapeutically or prophylactically effective amount of a compound of Claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/24664

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 31/4439; C07D 231/12
US CL : 514/341; 546/272.7
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/341; 546/272.7

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6,083,949 A (LIVERTON et al) 04 July 2000 (04.07.2000), column 2, lines 52-67, column 3, column49, lines 23-67.	7-16, 18-20

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
06 September 2002 (06.09.2002)

Date of mailing of the international search report
27 SEP 2002

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703)305-3230

Authorized officer
Rebecca L Anderson
Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/24664

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claim Nos.: 17
because they relate to subject matter not required to be searched by this Authority, namely:
because the claim is "use" claim which is an improper process claim lacking positive method steps.

2. ☒ Claim Nos.: 1-6
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Please See Continuation Sheet

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

Continuation of Box I Reason 2:
In these claims, the numerous variables (e.g. t, u, v, R1, R2, R2', R2'', R3-R17, X, Y, W, etc.) and their voluminous complex meanings and their seemingly endless permutations and combinations, make it virtually impossible to determine the full scope and complete meaning of the claimed subject matter. As presented, the claimed subject matter cannot be regarded as being a clear and concise description for which protection is sought and as such the listed claims do not comply with the requirements of PCT article 6. Thus it is impossible to carry out a meaningful search on same. A search will be made on the first discernable invention of claims 7-16 and 18-20, which is the products and methods of use for the first 7 compounds listed in claim 7.

Continuation of B. FIELDS SEARCHED Item 3:
CAS ONLINE
STN structure search